BETA-ADRENOCEPTOR BLOCKADE AND STIMULATION IN OBSTRUCTIVE LUNG DISEASE

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CHAPTER 1

INTRODUCTION

1.1. GENERAL INTRODUCTION AND AIM OF THE STUDY

"Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy."

Twenty-four years after this definition was stated by the American Thoracic Society (1962) it is still uncertain what the real mechanisms are which cause this disease. Morphological characteristics of asthma are hypertrophy and contraction of the bronchial smooth muscles, thickening of the basement membrane and edema of the airway wall with an infiltrate of inflammatory cells such as eosinophils and polymorphonuclear leucocytes (Clark and Godfrey, 1983). Furthermore, there may be submucosal gland hypertrophy and plugging of airways with viscid secretions containing desquamated epithelial cells and eosinophils. These pathological changes are found throughout the airways in fatal cases of asthma. It is uncertain, however, whether all these features are present in less severe attacks of asthma.

The pathogenesis of asthma is even more complicated and many aspects have not yet been elucidated. This is partly due to the fact that asthma is a multifactorial disease. Mechanisms which have been described as important in the pathogenesis of asthma include antigen-antibody reactions with release of bronchoconstrictor mediators from lung mast cells and other immunoreactive cells. Dysregulation of the autonomic nervous system has also been postulated. Respiratory heat loss, disturbances in ion and water concentrations and transport across the airway epithelium have been mentioned as aetiological factors in asthma induced by exercise.

Asthma, chronic obstructive bronchitis and emphysema belong to a group of pulmonary diseases often referred to as chronic nonspecific lung disease (CNSLD). This term was introduced by Orie et al. (1961) because these affections are often regarded as different manifestations of the same syndrome, in which the same underlying pathophysiological mechanisms play a role. Moreover, patients with CNSLD may show various disease symptoms and transitions of the clinical picture in the course of life.

We have focused our research on the autonomic regulation of the lung and airways in patients with CNSLD, with emphasis on the β-adrenergic system. This thesis presents studies concerning the effects of β-adrenergic blockade and stimulation on the lung function of patients with asthma and chronic obstructive bronchitis.

It is a well-known phenomenon that β-blockers can cause or aggravate asthma. This is mainly a problem of nonselective β-adrenoceptor antagonists, since β_1-adrenoceptor selective antagonists have a less marked bronchoconstrictor effect. Newly developed β-adrenoceptor antagonists have recently shown a high degree of β_1-adrenoceptor selectivity in animal experiments. To assess the β_1-adrenoceptor selectivity of two new β-blockers (bisoprolol and bevantolol) in man, their influence on bronchomotor tone and their interaction with the β_2-adrenoceptor agonist terbutaline was studied in patients with asthma (Chapters 4 and 6).

The effects of β-adrenoceptor-blocking agents on lung function can be enhanced by exercise. This phenomenon is probably caused by more effective β-blockade during a state of increased sympathetic tone. This rise in sympathetic tone due to exercise is also suggested to be responsible for the increase in forced expiratory airflow which can be demonstrated during exercise. We studied this hypothesis by measuring forced expiratory airflow at rest and during and after exercise in asthmatic patients both during placebo and during β-blockade (Chapter 6).

The influence of β-blockers on the lung function of patients with CNSLD is usually assessed by means of single-dose studies. This method has been criticized because multiple doses of β-blockers may have a more detrimental effect on the lung function of these patients. We therefore studied the effects of long-term treatment with metoprolol, a β_1-adrenoceptor selective blocker, and pindolol, a nonselective β-blocker with intrinsic sympathomimetic activity (ISA) in patients with CNSLD and concomitant hypertension. We also tried to establish whether the ISA of pindolol has a beneficial effect on lung function (Chapter 5).

In the literature there has been discussion whether the bronchoconstriction induced by β_1-adrenoceptor selective antagonists may be

caused by the possible presence of β_1-adrenoceptors in bronchial smooth muscles or by lack of selectivity of these β-blockers. To establish whether β_1-adrenoceptors play a role in bronchoconstriction or bronchodilatation, we studied the effects of the partial β_1-adrenoceptor agonist xamoterol on the lung function of asthmatic patients (Chapter 7).

Functionally, the airway system can be divided into central or large airways on the one hand and peripheral or small airways on the other.

From this point of view we attempted to establish whether β-adrenoceptor blocking and stimulating agents preferentially affect large or small airway function or induce a more generalized airway obstruction or dilatation respectively (Chapters 5, 6 and 8).

Before we present these studies, a general introduction of the autonomic regulation of the lung is given in Chapter 2, with emphasis on the β-adrenergic system. Thereafter, several methods are described in Chapter 3, to assess the effects of β-adrenoceptor agonists and antagonists on lung function parameters of large and small airways in patients with CNSLD.

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1.2. LIST OF ABBREVIATIONS

BP	blood pressure
CC	closing capacity
CNSLD	chronic nonspecific lung disease
CV	closing volume
CV (%)	coefficient of variation
Δ	change
ΔMEF_{50}	$\frac{MEF_{50}(He\text{-}O_2) - MEF_{50}(air)}{MEF_{50}(air)} \times 100\%$ = density dependence
EPP	equal pressure point
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
$He\text{-}O_2$	gas mixture of 80% helium and 20% oxygen
HR	heart rate
MEFV-curve	maximal expiratory flow-volume curve
MEF_{50}	maximal expiratory flow when 50% of the FVC remains to be expired
MEF_{25}	maximal expiratory flow when 25% of the FVC remains to be expired
N_2	nitrogen
P	pressure
PEFR	peak expiratory flow rate
Raw	total airway resistance
RV	residual volume
SEM	standard error of the mean
sGaw	specific airway conductance
TLC	total lung capacity
V	lung volume
$\dot{V}$	gas flow
VC	vital capacity
$V_{iso\dot{V}}$	volume of isoflow

CHAPTER 2

THE AUTONOMIC REGULATION OF THE LUNG AND AIRWAYS

2.1. INTRODUCTION

The autonomic regulatory system of the lung and airways consists of the parasympathetic cholinergic system and the sympathetic or adrenergic system; a third nervous system in the lung, known as the nonadrenergic, noncholinergic system, has also been described (Richardson and Béland, 1976; Richardson, 1979; Boushey et al, 1980; Nadel, 1980) (Fig. 1; next page).

With regard to the terminology it should be mentioned that "cholinergic" and "adrenergic" refer to the postganglionic nerve fibres, the neurotransmitter in both the parasympathetic and sympathetic ganglia being acetylcholine. However, the neurotransmitter in the postganglionic sympathetic junction at the end-organ is noradrenaline, whereas in the postganglionic parasympathetic junction the neurotransmitter is acetylcholine.

Since dysfunction of the autonomic regulation of the airways is thought to be one of the causes of asthma (Boushey et al, 1980; Nadel and Barnes, 1984), abnormalities in the β-adrenergic system may contribute to an abnormal function of the airways of asthmatic patients. Otherwise, it may be that asthma by itself can induce impairment of the function of the β-adrenoceptors in the airways.

β-Adrenoceptor antagonists, for instance, can cause bronchoconstriction in asthmatic patients (McNeill, 1964; Greefhorst, 1983) but not in normal subjects (Tattersfield et al, 1973; Woods et al, 1979). On the other hand, β-adrenoceptor agonists have proved to be the most powerful bronchodilators in asthma (Barnes et al, 1984), indicating good reactivity of the β-adrenoceptors in the airways of asthmatic patients.

In the following sections the three components of the autonomic regulatory system of the lung are discussed. It should be borne in mind that most of the present knowledge on the function of the autonomic nervous system in the lung has been obtained from animal studies, and there is considerable variation in airway innervation in different species (El-Barmini and Grant, 1975; Richardson, 1979; Partanen et al, 1982) and even within the same species (Woolcock et al, 1969a).

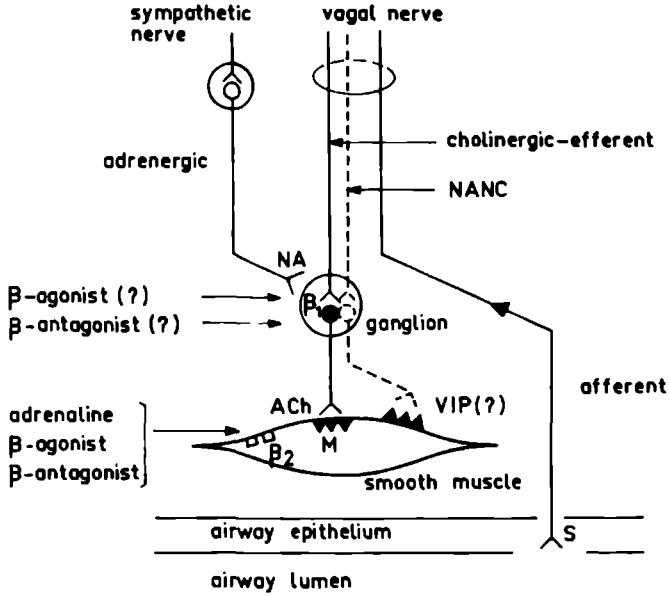

Figure 1. Autonomic regulation of bronchial smooth muscle tone.

A. **The cholinergic system.** Efferent nerve fibres synapse in cholinergic ganglia in the airway wall and postganglionic cholinergic fibres terminate on muscarinic receptors (M) with acetylcholine (ACh) as neurotransmitter. (Afferent fibres originating from sensory receptors (S) in the airway epithelium run through the vagal nerve to the central nervous system.)

B. **The nonadrenergic, noncholinergic system** (NANC). NANC nerve fibres probably travel through the vagal nerves, synapse in the ganglia in the airway wall, and terminate on receptors in the airway smooth muscle, possibly with vasoactive intestinal peptide (VIP) as neurotransmitter.

C. **The adrenergic system.** Adrenaline from the adrenal medulla and β-adrenoceptor agonists and antagonists interact via β_2-adrenoceptors (β_2) with the airway smooth muscle. Adrenergic nerve fibres originating from the sympathetic trunk ganglia, are supposed to terminate on β_1-adrenoceptors located on the cholinergic ganglia in the airway wall, with noradrenaline (NA) as neurotransmitter. Cholinergic nerve activity could in this way be modulated by adrenergic activity. It is suggested that β-adrenoceptor agonists and antagonists also interact with cholinergic nerve activity via β_1-and/or β_2-adrenoceptors on cholinergic ganglia or postganglionic nerves.

(Modified after Barnes, 1984a).

2.2. THE CHOLINERGIC SYSTEM

The airways are innervated by efferent cholinergic nerve fibres. Preganglionic fibres originating from the vagal nuclei travel through the vagal nerves to parasympathetic ganglia located in the airway wall and around the blood vessels. From these small ganglia postsynaptic fibres innervate the airway smooth muscles (Fig. 1), vasculature, submucosal glands and epithelium (Richardson, 1979; Nadel, 1980; Nadel and Barnes, 1984). Acetylcholinesterase-containing nerve fibres have been demonstrated mainly from the trachea to the larger bronchioli and in some animals down to the terminal bronchioli (El-Barmini and Grant, 1975; Nadel, 1980; Partanen et al, 1982). The postganglionic cholinergic fibres terminate on muscarinic receptors of the end-organs because neurotransmission can be blocked by antimuscarinic agents such as atropine (Nadel, 1984; Van Koppen et al, 1985). Electrical field stimulation of vagal preganglionic fibres causes bronchoconstriction, which effect can be inhibited by atropine (Widdicombe, 1962; Richardson, 1979; Nadel, 1980; Vermeire and Vanhoutte, 1979).

In normal human airways some resting bronchial tone is present, which is maintained by vagal nerve activity and hence can be blocked by atropine (Widdicombe, 1962; Nadel, 1980; Davis et al, 1982). Hyperactivity of the cholinergic system, on the other hand, can lead to increased bronchomotor tone and has therefore been described as an important mechanism in the pathophysiology of asthma (Boushey et al, 1980).

The cholinergic innervation of the lung appears mainly to be of importance in the larger airways, because stimulation of the vagal nerve leads to constriction of these larger airways but has little effect on smaller airways (Richardson, 1979). This appears to correlate with results of clinical studies showing that administration of parasympathicolytic agents such as atropine or ipratropriumbromide mainly causes dilatation of larger airways (Ashutosh et al, 1980; Minette et al, 1985). Moreover, direct receptor binding studies and autoradiography of mammalian lung have shown a high density of muscarinic receptors in smooth muscles of larger airways, while the receptor amount decreases when airways become smaller (Barnes et al, 1983a).

Woolcock et al (1969b), on the contrary, stated that in dogs vagal tone is present both in large and small airways, but is masked in the latter by adrenergic mechanisms.

It has been suggested that the parasympathetic ganglia and/or postganglionic fibres in the bronchial wall possess sympathetic nerve endings by which cholinergic neurotransmission can be modulated (Nadel, 1980; Gross and Skorodin, 1984; Barnes et al, 1984). Sympathetic neural activity and circulating adrenaline from the adrenal medulla or other β-adrenoceptor agonists could in this way influence cholinergic neurotransmission. The great effectiveness of the β-adrenoceptor agonists in asthma has, among other effects, been ascribed to such a modulating effect on the (hyper)activity of the cholinergic system (Vermeire and Vanhoutte, 1979; Barnes et al, 1984). The existence of adrenergic receptors or sympathetic nerve endings on postganglionic cholinergic neurons, however, is still uncertain (Nadel, 1980).

2.3. THE NONADRENERGIC, NONCHOLINERGIC SYSTEM

In 1976 Richardson and Béland described the existence of a third nervous system in the lung, which became known as the nonadrenergic, noncholinergic (NANC) system or nonadrenergic inhibitory system. While the cholinergic system is the excitatory nervous system of the lung, NANC nerves mediate relaxation of airway smooth muscles. Evidence of this inhibitory effect has been obtained from in-vitro experiments of animal and human airway smooth muscles (Richardson and Béland, 1976; Richardson, 1981; Taylor et al, 1984). Electrical field stimulation of airway smooth muscle with sufficient intrinsic tone resulted in a biphasic response: contraction was followed by relaxation. The contraction could be abolished by atropine, while the relaxation remained. The relaxant response persisted in the presence of a β-adrenoceptor antagonist, indicating its nonadrenergic character. Its neural nature has been deduced from the fact that the inhibitory effect can to some extent be blocked by neurotoxins such as tetrodotoxin. The nerves of this NANC system are supposed to run along the vagal nerves (Fig. 1).

The physiological or pathophysiological role of this system, however, is still unresolved and the neurotransmitter is yet to be identified. Vasoactive intestinal peptide (VIP) appears to be the most probable candidate (Barnes, 1984a).

A defect in the NANC system may contribute to increased bronchial hyperreactivity in asthma but this hypothesis is still unproven (Richardson, 1981; Barnes, 1984a).

2.4. THE ADRENERGIC SYSTEM

2.4.1. The adrenergic innervation of the lung

In contrast to the dense cholinergic nerve supply, the adrenergic innervation of the lung is sparse and there is considerable variation in the density of this adrenergic innervation between different species (Nadel, 1980). Richardson and Béland (1976) and Davis et al (1982) were unable to demonstrate any adrenergic innervation in human lung preparations. More recently, however, Partanen et al (1982) using a special histochemical method, demonstrated a small number of adrenergic nerves in human bronchial smooth muscle from lobar bronchi to terminal bronchioli. A larger number of adrenergic nerves was present in the bronchial vessels and submucosal glands. Results of a study by Zaagsma et al (1983), however, pointed to the absence of adrenergic innervation of human bronchial smooth muscle.

Electrical stimulation of the thoracic adrenergic nerves induces bronchodilatation in animals; this effect can be blocked by β-adrenoceptor antagonists (Cabezas et al, 1971; Nadel, 1980). This adrenergic bronchodilator effect, however, occurs only in the presence of vagal bronchomotor tone, for it disappears when the vagal nerves are cut (Cabezas et al, 1971). Moreover, complete inhibition of vagal induced bronchoconstriction could not be achieved by adrenergic nerve stimulation, indicating predominance of the vagal constrictor pathways to the airways (Cabezas et al, 1971). Isolated human airways, however, did not show such an adrenergic inhibitory response (Davis et al, 1982; Barnes, 1984b). Nevertheless, it has been suggested that

adrenergic nerves may modulate neurotransmission in the cholinergic ganglia located in the human airway wall (Barnes, 1984b; Fig. 1). Circulating catecholamines and β-adrenoceptor agonists could also interact with β-adrenoceptors on these ganglia and in this way attenuate the cholinergic, excitatory activity.

2.4.2. The adrenoceptors in the lung

2.4.2.1. Introduction

While adrenergic innervation is sparse or absent, there is a high density of adrenergic receptors (=adrenoceptors) in the lung and airways (Barnes et al, 1980 and 1982). Receptors can be defined as macromolecular structures on or in cells which serve as recognition sites for neurotransmitters, hormones or drugs. Receptor binding is followed by intracellular metabolic events which ultimately result in characteristic physiological or pharmacological effects (Ariens and Simonis, 1976; Lefkowitz et al, 1984). The magnitude of these effects depends on the affinity and the intrinsic activity of the agent that interacts with the receptor (Ariëns and Simonis, 1976). In this respect, drugs can be regarded as full agonists, partial agonists or full antagonists. A full agonist has affinity to the receptor and a high intrinsic activity, resulting in a maximal response after coupling to the receptor. A full antagonist has affinity to the receptor but lacks intrinsic activity and can prevent the action of an agonist by competition for the receptor site. A partial agonist has affinity to the receptor with a low intrinsic activity, which means that only part of the effect of a full agonist can be reached. A partial agonist can also behave as partial antagonist by displacing a full agonist from the receptor, resulting in a decrease of the response of the full agonist to the level of the maximal response of the partial agonist (Ariëns and Simonis, 1976; Ariëns, 1983).

In 1948 Ahlquist proposed the existence of two types of adrenergic receptors: α-adrenoceptors and β-adrenoceptors. Lands and coworkers in 1967 introduced a subclassification of the β-adrenoceptors in two

subtypes: the β_1- and the β_2-adrenoceptor. These authors postulated an absolute organ separation between the β_1- and the β_2-adrenoceptors. Several years later, however, it became clear that β_1- and β_2-adrenoceptors can coexist in the same tissue or organ and mediate the same physiological response (Carlsson et al, 1972). The relative distribution of β_1- and β_2-adrenoceptors varies from organ to organ, within one organ system in different species (Carlsson et al, 1972; Lulich et al, 1976; Minneman et al, 1979; Rugg et al, 1978), and within one organ system in the same species (Zaagsma et al, 1983). Ariëns and Simonis (1976) proposed a differentiation of the β-adrenoceptors in receptors for the neurotransmitter noradrenaline, hence called β_T-adrenergic receptors, and receptors for the hormone adrenaline, β_H-adrenergic receptors. This distinction of β_T- and β_H-adrenoceptors parallels the distinction of β_1- and β_2-adrenoceptors.

For the β_1-adrenoceptor the relative potencies of agonists are: isoprenaline > adrenaline = noradrenaline. For the β_2-adrenoceptor the relative potencies can be written as: isoprenaline > adrenaline >> noradrenaline (Minneman et al, 1979; Lefkowitz et al, 1984). For the α-adrenoceptors, too, a functional differentiation in α_1- and α_2-subtypes has been made (Berthelsen and Pettinger, 1977).

2.4.2.2. The α-adrenoceptor system in the lung

Although hyperresponsiveness of the α-adrenergic system in asthma has been suggested (Henderson et al, 1979; Nadel and Barnes, 1984), it is still controversial whether the α-adrenoceptors play an important role in the control of bronchomotor tone (Barnes, 1981a). Alpha-adrenoceptor agonists are able to induce bronchoconstriction in patients with obstructive lung disease but not in normal subjects. However, this only occurred when concomitantly a β-adrenoceptor antagonist with or without atropine was administered (Simonsson et al, 1972; Patel and Kerr, 1973). Recently, Goldie et al (1984) observed only weak α-adrenoceptor-mediated contractions of human isolated bronchi in 3 of 9 preparations tested. They concluded that α-adrenoceptors have no functional significance in isolated normal human bronchi. Bronchodilata-

tion caused by α-adrenoceptor antagonists in asthmatics has been mentioned, but this effect could also have been the result of other pharmacological actions of these drugs (Barnes, 1981a).

In a study by Shiner and Molho (1983), for instance, the α-antagonist phentolamine induced bronchodilatation in some asthmatics, in other patients no reaction at all, and in 2 patients even bronchoconstriction. The α_1-adrenoceptor antagonist prazosin did not cause a bronchodilatation in asthmatic patients at rest (Barnes et al, 1981a) but partially prevented the post-exercise bronchoconstriction in children with exercise-induced asthma (Barnes et al, 1981b). These authors suggested that this effect of prazosin may be due to blockade of α-adrenoceptors on mast cells, resulting in diminished release of bronchoconstrictive mediators by exercise. Otherwise, it might be that prazosin antagonizes α-adrenoceptor-mediated bronchoconstriction by an increase in noradrenaline during exercise. Recently, Jenkins et al (1985) demonstrated that inhaled prazosin partially protected subjects with bronchial hyperreactivity against histamine-induced bronchoconstriction.

Nevertheless, it seems that, at least for the time being, α-adrenoceptor antagonists are of minor importance in the treatment of patients with CNSLD.

2.4.2.3. The β-adrenoceptor system in the lung

Both β_1- and β_2-adrenoceptors are located on the cell membrane and stimulate the same biochemical effector, i.e. the adenylate cyclase system, which generates 3',5'-cyclic AMP (cAMP) (Lefkowitz et al, 1984). cAMP can be regarded as a second messenger, generating cellular processes which lead to the β-adrenoceptor mediated effects. After coupling of the agonist or hormone (H) to the receptor (R) a receptor-hormone complex (HR) is formed which consecutively binds a guanine nucleotide regulatory protein (N). This results in conversion of the receptor from a state of low affinity for the hormone to a high affinitity state which binds the hormone tightly (HRN complex). Guanosine triphosphate (GTP) binds to the HRN complex and activates N. This re-

sults in the formation of a N-GTP complex which activates adenylate cyclase, which in turn catalyses the conversion of adenosine triphosphate in cAMP (Lefkowitz et al, 1984).

The density and the characteristics of receptors can be demonstrated by means of radioligand binding studies and autoradiography.

In radioligand binding studies, radioactively labelled adrenoceptor antagonists such as ^{3}H-dihydro-alprenolol or ^{125}I-iodocyanopindolol, bind to adrenoceptors on the cell surface. β-Adrenoceptor affinity and density can be determined by this method. Moreover, differentiation between β_1- and β_2-adrenoceptor subtypes is possible by using selective agonists and antagonists (Fig. 2) (Rugg et al, 1978; Barnett et al, 1978; Barnes et al, 1980).

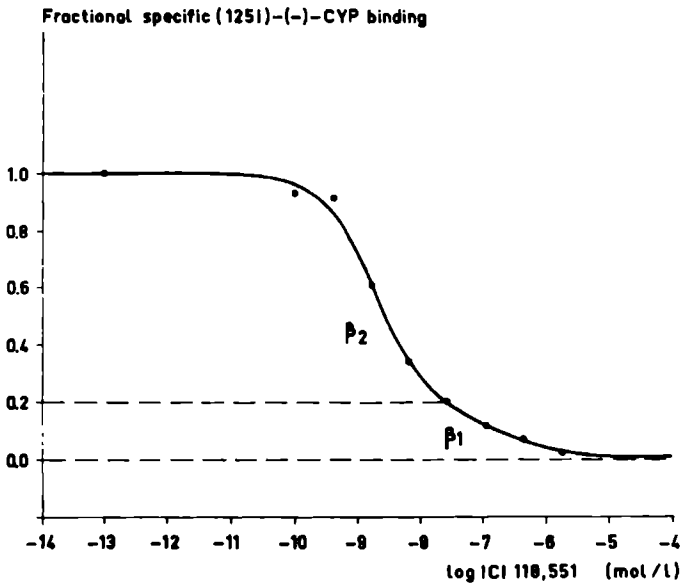

Figure 2.
Competition of the β_2-adrenoceptor selective antagonist ICI 118, 551 for (^{125}I)-(-)-Cyanopindolol (CYP) binding sites on membrane homogenates of normal human lobar bronchus tissue.

ICI 118,551 displaces (^{125}I)-(-)-CYP from the β-adrenoceptors in the tissue homogenates in a dose-dependent manner. From the shape of the curve it can be concluded that both β_2- and β_1-adrenoceptors are present in human lobar bronchus tissue. The ratio of β_2:β_1-adrenoceptors is approximately 4:1.
(This figure was kindly provided by Ch. van Koppen, Dept. of Pharmacology, University of Nymegen.)

A disadvantage of the radioligand binding technique is that tissue homogenates are generally used, which makes it difficult to assess receptor density on different cell types (Barnes, 1984b). More recently, however, autoradiography has been introduced as a semiquantitative method to determine the density of receptors on different cell types (Scott Young and Kuhar, 1979; Barnes et al, 1982/1983a). The principle of this method is that slide-mounted sections of a tissue are incubated with a radioligand. Next, coverslips coated with a photographic emulsion, are fixed on these slides and after a certain exposure time the receptors bound by the radioligand can be localized in the tissue sections (Scott Young and Kuhar, 1979). Both techniques have been used to localize β-adrenoceptors in mammalian lung and to differentiate between the β_1- and the β_2-subtypes (Rugg et al, 1978; Barnett et al, 1978; Barnes et al, 1980; Barnes et al, 1982/1983a).

With regard to the human lung it appears that the ratio of β_2- to β_1-adrenoceptors is approximately 3:1 (Carstairs et al, 1985) or 4:1 (Fig. 2); these ratios have also been demonstrated in other species (Rugg et al, 1978; Barnett et al, 1978; Barnes et al, 1983b). Carstairs et al (1985) demonstrated by means of autoradiography that β-adrenoceptors occur not only on human airway and vascular smooth muscles but in even higher densities on airway epithelium, submucosal glands and alveolar walls. They demonstrated a homogeneous population of β_2-adrenoceptors on airway smooth muscles of large and small airways, on airway epithelium, and on vascular smooth muscles. This was confirmed in functional studies for human airway smooth muscles by others (Zaagsma et al, 1983). Bronchial submucosal glands and alveolar walls appeared to contain both β_1- and β_2-adrenoceptors.

The β-adrenoceptor density in the airway smooth muscle increases from large to small airways (Carstairs et al, 1985) as has also been shown for the ferret (Barnes et al, 1983a).

Adrenoceptor density is regulated by a variety of physiological and pathophysiological processes (Lefkowitz et al, 1984; Venter and Fraser, 1985). Adrenergic agonists and antagonists and hormones such as glucocorticoids and thyroid hormone can also influence adrenoceptor density. The beneficial effects of glucocorticoids during an asthmatic attack, for example, have been attributed to an increase in β-adreno-

ceptor density (Venter and Fraser, 1985).

These authors also demonstrated autoantibodies against β-adrenoceptors (Fraser et al, 1981) and they suggested that in some asthmatics autoantibodies to β_2-adrenoceptors may mediate a state of "β-adrenergic hyporesponsiveness". Since these autoantibodies were also demonstrated in plasma of apparently normal subjects, it is still uncertain whether they are important in asthma.

Szentivanyi (1968) postulated impaired β-adrenoceptor function as a fundamental factor in the aetiology of asthma. A reduced number and function of β-adrenoceptors on circulating blood cells of asthmatics has indeed been demonstrated (Brooks et al, 1979; Tashkin et al, 1982). Nevertheless, the hypothesis of Szentivanyi has been questioned because the decrease in β-adrenoceptor density in these patients was at least partly due to chronic β-adrenoceptor agonist treatment, which results in desensitization or down-regulation of the adrenoceptor density of the cell (Galant et al, 1980; Djurup, 1981). Desensitization involves a reversible loss of receptor responsiveness which can be the consequence of overstimulation by agonistic drugs (Djurup, 1981; Lefkowitz et al, 1984).

Several clinical studies of the effects of chronic treatment with bronchodilators on the response to a β-adrenoceptor agonist in asthmatic patients have not yielded arguments for an attenuation of this response (Larsson et al, 1977; Harvey and Tattersfield, 1982; Tattersfield, 1985). The process of desensitization therefore appears not to be of clinical relevance in the treatment of patients with CNSLD with β-adrenoceptor agonists.

Additional information on the function of β-adrenoceptors in the lung and airways can be obtained by functional in-vitro studies, e.g. by contraction and relaxation of airway smooth muscles. Some results of such studies of human bronchial tissue are now available (Zaagsma et al, 1983; Goldie et al, 1984), but further results are to be awaited.

The function of the β-adrenergic system in the lung can also be studied by investigating the effects of β-adrenoceptor agonists and antagonists on various pulmonary functions. Since β-adrenoceptors re-

gulate several processes in the lung and airways, β-adrenergic drugs can influence these biological processes. Some of these effects of β-adrenoceptor agonists and antagonists are listed in the table (next page). Most of the information on β-adrenoceptor functions, however, is obtained from animal studies, mainly because of technical problems. Several effects of β-adrenergic agonists and antagonists are still to be clarified.

As mentioned before, β-adrenoceptor antagonists can cause bronchoconstriction in patients with asthma. Since atropine can reduce this increase in airway resistance (MacDonald et al, 1967; Grieco et al, 1971), it appears that unopposed cholinergic activity is the main cause of β-blocker-induced bronchoconstriction. From results of animal experiments it has been suggested that β-blocking agents also cause bronchoconstriction by inhibition of adrenergic modulation of cholinergic tone (Cabezas et al, 1971). If this mechanism exists in man as well, it may be possible that both β-adrenoceptor agonists and antagonists, apart from a direct effect on airway smooth muscles, also have an effect on cholinergic ganglia or postganglionic fibres in the airway wall (Fig. 1).

McLagan and Ney (1979) demonstrated in guinea pigs and rats a 50% reduction in propranolol-induced bronchoconstriction after intravenous administration of disodium cromoglycate. Koëter et al (1982) found in asthmatic patients a protective effect of cromoglycate against bronchoconstriction induced by inhalation of propranolol. Since it is assumed that cromoglycate is an inhibitor of mediator release from lung mast cells, it could be that β-adrenoceptor antagonists also cause bronchoconstriction by release of mediators from lung mast cells.

β-Adrenoceptor agonists mainly cause bronchodilatation by a direct effect on the β_2-adrenoceptors in the airway smooth muscles. Like the bronchoconstrictor effect of β-adrenoceptor antagonists the bronchodilator effect of β-adrenoceptor agonists can be demonstrated easily in man by measuring lung function parameters, as described in Chapter 3.

TABLE Effects of β-adrenoceptor agonists and antagonists on various structures and cell types of the lung

Structure/ cell type	adrenoceptor subtype	β-agonist	β-antagonist
Airway smooth muscle	β_2	relaxation	contraction
Mast cell	β_2	inhibition mediator release	degranulation
Vascular smooth muscle	β_2	relaxation	contraction
Parasympathetic ganglia/nerves	β_1* β_2*	transmission inhibition*	transmission enhancement*
Submucosal gland	$\beta_2 >> \beta_1$	increase mucus secretion	no influence
Airway epithelium	β_2	increase fluid+ ion transport	*
		increase in mucociliary clearance	decrease
Alveoli	$\beta_2 >> \beta_1$	increase surfactant release; increase in lung fluid absorption	*
		*	decrease in gas exchange

* still to be clarified.

Modified after Barnes, 1984b. (For other references see also Gatto et al, 1984).

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CHAPTER 3

BETA-ADRENOCEPTOR AGONISTS AND ANTAGONISTS AND THEIR EFFECTS ON DYNAMIC LUNG FUNCTION PARAMETERS IN PATIENTS WITH CNSLD

Soon after the introduction of nonselective β-adrenoceptor antagonists it became clear, that these drugs can induce severe bronchospasm in asthmatic patients (McNeill, 1964). β-adrenoceptor agonists on the other hand can induce bronchodilatation as has been described in Chapter 2. These changes in airway calibre can be measured as a change in a) airway resistance, b) airflow, c) expired volume.

A schematic representation of the airway system is shown in Figure 1.

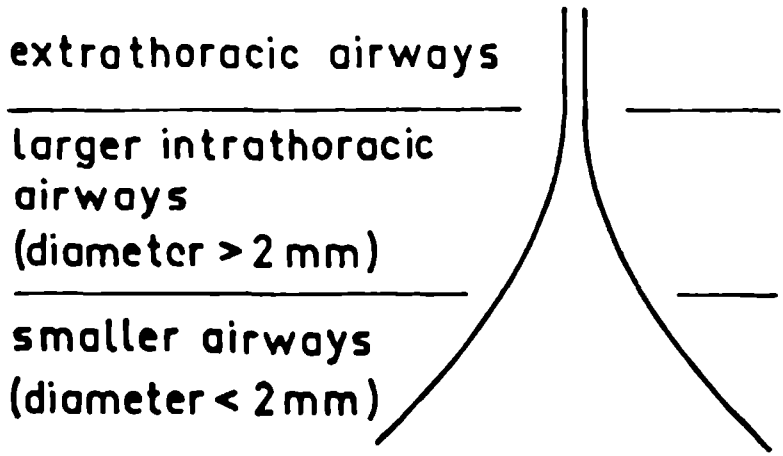

Figure 1 Schematic representation of the airway system. The total cross sectional area of the extrathoracic airways and trachea is 2.5 cm^2, of the larger intrathoracic airways approximately 40 cm^2 and of all alveolar ducts and sacs about 70 m^2.

The total cross sectional diameter of the airways increases from the mouth to the alveoli. The total flow resistance is therefore high in the trachea and extrathoracic airways, somewhat lower in the larger intrathoracic airways and resistance decreases rapidly towards the periphery of the lung. Because airflow and total airways diameter are inversely related to each other, airflow is high in extrathoracic and larger intrathoracic airways and low in smaller airways.

Several methods for assessment of the effects of β-adrenoceptor agonists and antagonists on airway resistance and airflow will be discussed in this Chapter, as is summarized in the Table.

Table Summary of lung function parameters, assessment procedures and their main sensitivities for large and/or small airways function.

Lung function parameters	Assessment procedure	Large airways and/or small airways function
Total airway resistance	. body plethysmograph . forced oscillation technique . interrupter technique	mainly large airways function
Peak expiratory flow rate	. peak flow meter . pneumotachograph	large airways function
Forced expiratory volume in 1 sec	. spirometer . pneumotachograph	mainly large airways function
Closing volume	. single breath N_2-washout technique	small airways function
Frequency dependence of lung compliance	. esophageal balloon + pneumotachograph	small airways function
Flow-volume curve	. pneumotachograph	large and small airways function

For explanation of lung function parameters and assessment procedures: see text.

First, measurement of total airway resistance, peak expiratory flow rate and the forced expiratory volume in one second are described, as these parameters are thought to reflect mostly large airways function.

From studies of "healthy" smokers without signs of chronic nonspecific lung disease (CNSLD) it became clear that with conventional lung function tests changes in airway calibre could not be assessed;

however, with more sophisticated methods changes in the calibre of small, peripheral airways could be demonstrated (Buist and Ross, 1973; Dosman et al, 1975; Martin et al, 1975). Since the introduction by Mead et al (1967) of the "equal pressure point" concept, it appears that the airway system functionally can be divided into a more central part on the one hand, and a more peripheral part on the other hand. Via pathological studies it became clear, that there is also a morphological substrate for the changes in small airways function and the concept of "small airways disease" was developed (Hogg et al, 1968; Cosio et al, 1977; Petty et al, 1980). These peripheral airways are anatomically defined as the airways with a diameter of 2 to 3 mm or less. Aerodynamically small airways are those in which airflow is laminar in contrast to the more turbulent flow in the larger airways during forced expiratory manoeuvres (Ingram and McFadden, 1979). Several studies dealing with small airways dysfunction have been directed to discover early changes in airflow, e.g. in smokers and industrial workers (Martin et al, 1975; Brown et al, 1977, Nemery et al, 1981; Cotton et al, 1982). In the last decade there has also developed an increasing interest in performing these tests to discriminate between the effects on large and small airways function of bronchoconstrictor and bronchodilator agents (Ingram et al, 1977; Brown et al, 1977; Chan-Yeung et al, 1976; Ashutosh et al, 1980).

Measurements of closing volume and frequency dependence of lung compliance are two tests which are used to discover changes in small airways function when other lung function tests are still normal.

Finally, the flow-volume curve is discussed as a relatively simple lung function test, which is suited to measure simultaneously large and small airways function.

3.2. ASSESSMENT OF LARGER AIRWAYS FUNCTION

3.2.1. Measurement of total airway resistance

The measurement of airway resistance (Raw) is usually performed with a body plethysmograph (Dubois et al, 1956a). This method has the advan-

tage that thoracic gas volume (TGV) can be measured at the same time. As airway resistance varies with lung volume, this resistance is usually expressed as a conductance/volume ratio. Airway conductance (Gaw) is the reciprocal of airway resistance and when TGV is known specific airway conductance (sGaw) can be calculated: $sGaw = \frac{Gaw}{TGV}$ (Briscoe and Dubois, 1958; Tattersfield and Keeping, 1979).

In contrast to the methods discussed below measurement of Raw is relatively easy to do, even for dyspnoeic patients and this procedure also excludes the contribution of dynamic compression of the airways as occurs during a forced expiration manoeuvre. Another advantage of this method is its great sensitivity to detect changes in airway calibre. It does, however, not distinguish between the contribution of extrathoracic and intrathoracic airways to total airway resistance, which is particularly disadvantageous in assessing airway responses of pharmacological agents (Ingram and McFadden, 1977). Also the reproducibility of measuring Raw with the body plethysmograph is probably not very good: there is a high within-subject variability with mean values for the coefficient of variation between 10% and 20% with a large range which necessitates several measurements (5-10) (Pelzer and Thompson, 1966).

Raw can also be determined with the **forced oscillation technique** as described by DuBois et al (1957b), which method might have a better reproducibility (Tattersfield and Keeping, 1979). This technique has the advantage over the body plethysmograph that the necessary equipment is much cheaper. However, forced oscillation has not been used frequently yet to assess airway responses to pharmacological agents.

Recently, the **interrupter technique**, as described in 1954 by Mead and Whittenberger to measure total airway resistance has gained new interest (Jackson et al, 1974; Shaw et al, 1983). This method, however, seems to be less useful in bronchial challenge testing, since its validity in severely obstructed patients has been described controversially (Eiser et al, 1983).

Measurement of Raw is often used in the assessment of broncho-

dilatation by β-adrenoceptor agonists and bronchoconstriction by β-adrenoceptor antagonists in patients with CNSLD. Tattersfield and coworkers (1979 and 1983) have also used the plethysmographical assessment of Raw as a sensitive method to determine the β_1-adrenoceptor selectivity of different β-adrenoceptor antagonists in healthy subjects. For this purpose they compared the displacement of sGaw dose-response curves with a β_2-adrenoceptor agonist during different types of β-blockers. The main objective for performing these test in normal subjects was to avoid side effects of β-blockers in patients with CNSLD. Although this method seems to be suitable for assessing the β_1-adrenoceptor selectivity of β-blockers, it does not give full information of the bronchoconstrictor effects of β-blocking agents in patients with CNSLD, because β-blockers do not cause bronchoconstriction in normal subjects (Kumana and Ruffin, 1978; Woods et al, 1979).

3.2.2. Peak expiratory flow rate

Soon after the introduction of the peak flow meter in 1959 by Wright and McKerrow measurement of peak expiratory flow rate (PEFR) became one of the most popular methods to assess airway responses to pharmacological agents. The great advantage of PEFR measurement is the simplicity for patient and investigator. It is also the only practical method at this moment to assess the lung function of the patient at home (Pride, 1979), which can be very helpful to detect a diurnal rhythm in the airway conductance of the asthmatic patient. This method can effectively be used to evaluate short-term and long-term effects of medication on pulmonary function of patients with CNSLD, both in hospitalized patients and in situations outside the hospital. PEFR-measurement seems to be good reproducible. McCarthy et al (1975) measured a coefficient of variation (CV) for this parameter of 5 to 6% in normal subjects. Nickerson et al (1980) measured for PEFR a CV of 5.8% in normals and of 6.6% in patients with cystic fibrosis. In one of our studies (Chapter 4) we found a within-subject CV of 5.8 $\pm$ 3.5% (mean $\pm$ SD) in asthmatic patients during a stable stage of their disease as assessed with the Wright peak flow meter (Fig. 2, left panel).

However, the value of PEFR can show false high readings due to dynamic compression of the airways. This phenomenon can be unmasked by taking flow-volume curves (see Paragraph 3.4).

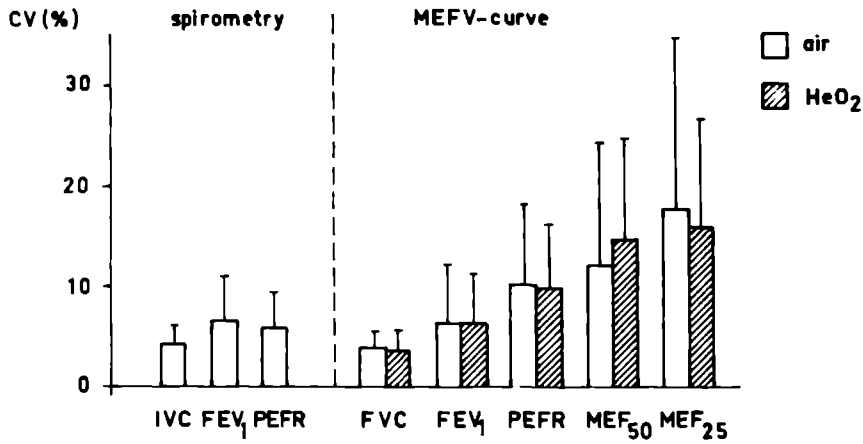

Figure 2 Coefficients of variation (CV) for intrasubject reproducibility of lung function parameters in asthmatic patients during a stable phase of their disease.
Left panel: mean CV (±SD) of parameters as measured with spirometry on 4 different days in 8 patients.
Right panel: mean CV (±SD) of parameters as measured with MEFV curves on 3 different days in 11 patients when breathing air and a helium-oxygen (HeO_2) mixture.

3.2.3. Forced expiratory volume in one second

The forced expiratory volume in one second (FEV_1) can be assessed by spirometry or can be derived from flow-volume curves (see Paragraph 3.4). Like peak flow rate the measurement of FEV_1 is easy to perform. It is one of the most reproducible lung function parameters: within-subject coefficients of variation vary from 2.5 to 5.3% (Nickerson et al, 1980). We found a CV for FEV_1 of 6.4 ± 4.6% (mean±SD) as assessed by spirometry and of 6.2 ± 6.1% when FEV_1 was derived from flow-volume curves (Fig. 2). The FEV_1 appears to have a lower sensitivity in de-

tecting changes in airway calibre due to bronchoconstrictor agents than other lung function tests. It is, however, the most specific test for assessment of bronchoconstriction (Michoud et al, 1982). It has to be therefore one of the mainstays in the assessment of ventilatory effects of β-adrenoceptor agonists and antagonists in man.

The fact that β-adrenoceptor antagonists do not affect FEV_1 in normal subjects should caution against drawing too many, if any, conclusions from studies of ventilatory effects of β-blockade in normal men. Like PEFR, FEV_1 is relatively insensitive to changes in the peripheral airways.

FEV_1 and PEFR are both assessed during a maximal expiratory manoeuvre after a preceding maximal inspiration. Particularly this deep inspiration can by itself have an effect on bronchomotor tone (Nadel and Tierney, 1961; Gayrard et al, 1975; Fish et al, 1977; Orehek et al, 1980), possibly induced by a vagal reflex mechanism or via a local mechanism in the airway smooth muscle (Zamel, 1984). In normal subjects at rest the inspiratory manoeuvre has no effect, however, during pharmacologically induced bronchoconstriction it can cause in the same subjects without CNSLD a bronchodilatation (Fish et al, 1977). In asthmatic patients on the other hand the effects of deep inspiration are variable: at normal resting conditions it can cause an increase in airway resistance (Gayrard et al, 1975; Orehek et al, 1980), whereas after inhalation of bronchoconstrictor pharmacological agents the effect of the deep inspiratory manoeuvre is unpredictable, varying from bronchoconstriction to bronchodilatation (Fish et al, 1977).

With regard to the effects of β-blockade on lung function, there are at present few data available concerning the combined effects of systemically administered β-adrenoceptor antagonists and the manoeuvre of deep inspiration on bronchomotor tone in patients with CNSLD. Gayrard et al (1975) found only in 4 out of 14 asthmatic patients a potentiation of the bronchoconstrictor effect of intravenously administered propranolol, as measured by an increase in specific airway resistance, by the inspiratory manoeuvre. There was, however, no significant mean increase in the effect of deep inspiration on airway resistance after propranolol in comparison with the control group.

Moreover, as stated by Orehek (1982), the use of maximal expiratory

manoeuvres for measurement of bronchoconstrictor effects of pharmacological agents is only misleading in those asthmatics in whom deep inspiration causes bronchodilatation, which may leave the FEV_1 e.g. erroneous unchanged.

3.3. ASSESSMENT OF SMALLER AIRWAYS FUNCTION

3.3.1. Closing volume

The **single-breath nitrogen washout technique** has gained a lot of interest for the detection of peripheral airways obstruction. Buist and Ross (1973) stated that it can be used to evaluate three aspects of lung function: uniformity of alveolar ventilation, residual volume and the lung volume at which dependent lung zones cease to ventilate (closing volume). The advantage of this test is, that it is relatively easy to perform: after a deep inspiration of 100% oxygen or a tracer gas to total lung capacity (TLC), a slow expiratory vital capacity (VC) follows during which the concentration of nitrogen or tracer gas is recorded versus expired volume (Fig 3) (next page).

The slope of the alveolar plateau (Phase III) is determined and also the increase in nitrogen concentration (percent) per liter ($\Delta N_2/l$). The closing volume (CV) has been defined as the difference between residual volume (RV) and the transition between the alveolar plateau (Phase III) and the last steep part of the nitrogen washout curve (Phase IV). Closing volume is usually expressed as percentage of VC: CV/VC%. Closing capacity (CC) being the gas volume in the lung at the transition between Phases III and IV, is also used and expressed as percentage of TLC: CC/TLC%. (For a more detailed description of this test, see Sterk, 1981.)

Several studies have demonstrated the usefulness of this test as a method to detect small airways dysfunction (Gelb and Zamel, 1973; Cochrane et al, 1974; McFadden et al, 1974; Nemery et al, 1981). Data concerning the correlation between pathological changes in small airways and abnormalities in the slope of Phase III and/or closing volume are conflicting. Cosio et al (1978), for instance, found a good corre-

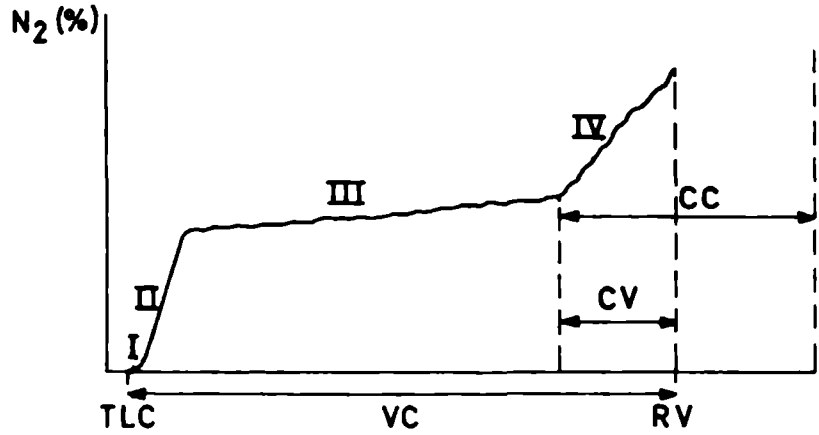

Figure 3 Closing volume measurement by the single-breath N2 washout technique.
Phase I: dead space gas; phase II: gas from dead space and alveolar gas; phase III: alveolar gas ("plateau"); phase IV: closure of small airways in the dependent lung zones, while upper lung zones, with a high N2-concentration, are still emptying. Closing volume (CV) is defined as the volume above RV at which phase IV begins.

lation between pathological and physiological changes in a group of 36 patients undergoing thoracotomy of whom 34 were smokers. Berend et al (1981b) on the contrary, were not able to demonstrate such a correlation. They suggested that these differences may be the result of a different method of fixation of the excised lungs.

Although the simplicity of this method seems to be an advantage, the performance has to be done very properly, otherwise the within-subject variability will be too high (McFadden et al, 1975), especially when this method is to be used to detect differences in effects of bronchodilator and/or bronchoconstrictor agents on small airways function.

3.3.2. Frequency dependence of compliance

Lung compliance is a measure of the distensibility of the lungs and it is defined as the change in lung volume per unit change in transpulmonary pressure. This pressure difference between mouth and pleural space is measured with a balloon in the lower part of the esophagus. At the same time, the change in volume is measured at the mouth from which the change in lung volume can be derived. By plotting change in lung volume (ΔV) against change in transpulmonary pressure (ΔP) pressure-volume (P-V) curves are constructed from which lung compliance ($\Delta V/\Delta P$) can be calculated. Static lung compliance can be determined from P-V curves when airflow is zero. Since this is difficult to perform, usually the semistatic compliance is measured by making a slow expiratory vital capacity manoeuvre. From P-V curves during different breathing frequencies dynamic compliance can be determined.

Frequency dependence of dynamic lung compliance was first described by Woolcock et al (1969) as a sensitive method to discover small airways dysfunction when routine lung function tests are within normal limits. They reasoned that, if static lung compliance (C_{st}) as determined by the static pressure-volume curve, and total pulmonary resistance are normal, a fall in dynamic compliance (C_{dyn}), expressed as the ratio $\frac{C_{dyn}}{C_{st}}$, with increasing respiratory frequency will be the result of an increasing abnormality in ventilation distribution in the lung, which may well be caused by small airways obstruction. They showed that in bronchitic and asthmatic patients C_{dyn} was frequency dependent in contrast to normal subjects and remained so, though to a lesser extent after a β-adrenoceptor agonist. Later on, several other authors (Rubin et al, 1974; Gelb and Zamel, 1973; Martin et al, 1975) have used the assessment of frequency dependence of C_{dyn} as a test for small airways obstruction. It appears to be a very sensitive test to detect early pathological changes in peripheral airways (McFadden et al, 1974; Buist, 1984).

3.4. THE FLOW-VOLUME CURVE

3.4.1. Introduction

The assessment of small airways obstruction with tests like the frequency dependence of compliance and the measurement of closing volume has one major objection: abnormal results obtained with these tests are only indicative for small airways disease in the presence of normal values for elastic lung recoil (i.e. normal static compliance), FEV_1, specific airways conductance and other parameters of large airways function. By measuring flow and volume during a maximal expiration manoeuvre (MEFV-curve), especially with the use of gases of different densities and viscosities, it became possible to determine changes in small airways function even when routine lung function tests are abnormal (McFadden and Ingram, 1982).

While with spirometry lung function is measured by recording in- and/or exhaled volume against time, lung function can also be assessed by plotting flow (V in l/sec) against volume (V in l), which yields the flow-volume curve. Usually flow and volume are recorded during a forced vital capacity manoeuvre. Parameters obtained from this MEFV curve are determined by lung elasticity and mechanical properties of the intrathoracic airways like static dimensions and dynamic narrowing during expiration (Mead et al, 1967; Ingram and McFadden, 1977; Pride, 1979).

Changes in calibre of extrathoracic airways do not influence the late expiratory part of the MEFV-curve. An example of a MEFV-curve is shown in Fig 4 (next page). The inspiratory part of the curve (lower panel) is mostly determined by abnormalities in structure and/or function of the upper(extrathoracic) airways. As we are mainly interested in responses of the intrathoracic airways to β-adrenergic agents, this inspiratory part of the curve will not be discussed further.

3.4.2. The composition of the MEFV-curve

The MEFV-curve can be divided into two phases (Schilder et al, 1963;

Knudson et al, 1976a/b; Bouhuys, 1977); an initial effort dependent phase which comprises the first 20 to 30% of the expired forced vital capacity (FVC) after inhalation to TLC-level. PEFR and to a certain extent also FEV_1, are determined during this phase. This phase of expiratory flow is mostly dependent on the effort of the expiratory muscles and resistance of the total pulmonary system (Schilder et al, 1963). The second phase of the MEFV-curve demonstrates the expiratory

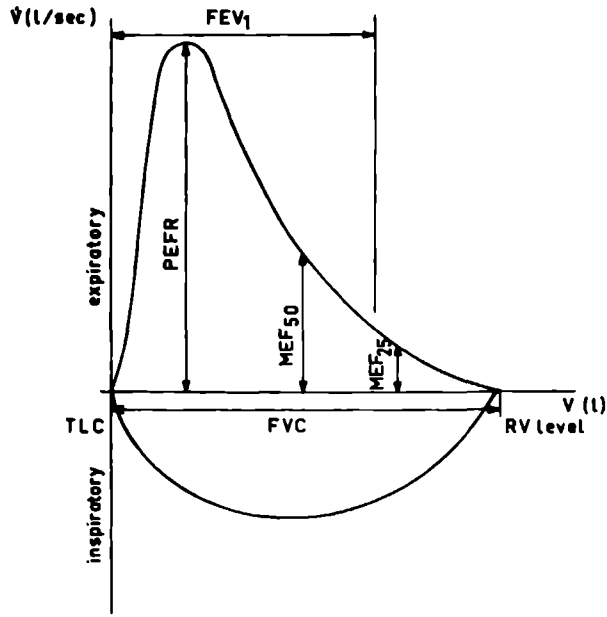

Figure 4 Maximal expiratory flow-volume curve.
For abbreviations see list of abbreviations (page 13).

flow of the late two-third part of the FVC and is less effort dependent. MEF_{50} and MEF_{25}, being the maximal expiratory flow when 50% and 25% of the FVC respectively, still have to be expired, are the main parameters of this phase (Fig 4). This late phase of expiratory flow is mainly determined by elastic lung recoil, properties of the respired gas and resistance of smaller airways (Schilder et al, 1963; Mead et al, 1967). Especially the flow at lower lung volumes as represented by MEF_{25}, is thought to reflect small airways function (Mead et al, 1967). As acute changes in lung elasticity are rare (Gold et al,

1967; Pride, 1979), short-term changes in MEF_{50} and MEF_{25} by bronchoconstrictor or bronchodilator agents are indicative for changes in small airways calibre (Bouhuys et al, 1969).

There is still some discussion on the best method of reading the MEFV-curve with regard to the amount of curves which have to be performed and from which curve the parameters should be recorded. Most authors (Peslin et al, 1979; Schrader et al, 1983; Johansen and Vale, 1984) agree that three consecutive curves are sufficient. Parameters can be derived from the "envelope-curve", which means that the curves are superimposed, preferentially at TLC level, and one composite curve is constructed (Peslin et al, 1979; Schrader et al, 1983). The American Thoracic Society on the other hand has proposed that all indices should be taken from the curve yielding the largest sum of FVC and FEV_1 (Gardner, 1979).

3.4.3. Methods for assessing expiratory flow-volume curves

3.4.3.1. Spirometry

Spirometers record expired volume against time. From these curves flow rates can be obtained by differentiation (Bouhuys, 1977). The inertia of a spirometer, however, is usually too high to record high flow rates correctly.

3.4.3.2. Pneumotachography

With pneumotachography it is possible to measure instantaneously airflow and volume (Dawson, 1982; Teculescu, 1985). The pneumotachograph consists of a bundle of narrow parallel tubes ("Fleisch") or a fine mesh metal gauze ("Lilly"), placed in the airstream. This causes laminar flow and a resistance to airflow which has to be minimal, though sufficient enough to induce a pressure-gradient across the resistance. This pressure difference is measured by a differential pressure transducer, and from the output signal flow and volume (integrated flow) can be deduced and plotted against each other on an oscilloscope or X-

Y recorder. For laminar airflow the pressure gradient (ΔP) is defined by the Poiseuille equation: $\Delta P = \frac{8.l.\eta.\dot{V}}{\Pi r4}$

wherein $\dot{V}$ = flow of the gas;

η = viscosity of the gas;

l = length of tube] whereover ΔP is measured.

r = radius of tube]

As can be concluded from this equation, a linear relationship exists between the pressure difference (ΔP) and airflow ($\dot{V}$). This linearity, however, is only valid when flow is laminar.

When airflow becomes turbulent, the pressure-flow relationship becomes curvilinear. Contrary to laminar airflow, turbulent flow is not only dependent upon viscosity of the gas but also upon the density of the gas. The flow above which turbulence occurs can be deduced from the Reynolds number: $Re = \frac{2\ v\ r\ \rho}{\eta}$

where v = velocity of flow;

ρ = density;

η = viscosity of the gas;

r = radius of the tube.

Above or below a critical value of the Reynolds number gas flow becomes turbulent or laminar respectively. For instance for airflow in a long smooth-walled cylindrical tube the critical value of Re is 2000.

When turbulence occurs the Rohrer equation can be applied:
$\Delta P = k_1 \dot{V} + k_2 \dot{V}^2$ in which k_1 and k_2 are constances related to viscosity and density of the gas respectively. As can be seen from this equation the resistance is proportional to the flow squared and therefore considerably higher than in laminar flow.

When applying these pressure-flow relationships to the airflow in the airways difficulties arise, because in the bronchial tree with its branches and irregular surface varying airflow profiles develope. In the upper, extrathoracic airways there exists a very complex flow pattern. In the trachea and the large bronchi airflow is presumed to be

mainly turbulent during forced expiration. In the smaller bronchi (down to the 12th generation) (Bouhuys 1977) the Reynolds number of airflow is below 2000 and hence airflow is laminar. From the smaller airways down to the alveoli gas is transported by diffusion.

3.4.4. The phenomenon of density dependence

Differentiation between airway obstruction in the airways with turbulent flow on the one hand and those with laminar flow on the other hand became possible by the introduction of measuring MEFV-curves when breathing gases with different densities and viscosities.

Changes in density of the respired gas have their largest effects on that part of the MEFV-curve which is limited mostly by turbulence, i.e. that part with the highest linear velocity: PEFR and FEV_1. Consequently, breathing a gas with low density and high viscosity will lower the Reynolds number and airflow becomes more laminar. If, in the air breathing situation, the forced expiratory flow was predominantly limited by turbulence in the larger airways, then the same manoeuvre with a low-density gas will yield much higher peak flow rate and FEV_1 values. However, if the forced expiratory flow is limited by obstruction in the peripheral airways (where no turbulence occurs in any situation) a low-density gas will not change the forced expiratory flow parameters very much.

Since the slopes of the MEFV-curve around PEFR and FEV_1 are very steep, small changes in horizontal position of these parameters on the MEFV-curves will have tremendous effects when comparing curves breathing air and a low-density gas. Therefore, parameters in the less steep parts of the MEFV-curves are compared: MEF_{50} and MEF_{25}. The difference in flow between two gases with different densities is called "**density dependence**"(Ingram and McFadden, 1977; Teculescu et al, 1982; Bogaard et al, 1982). This density dependence is usually measured by comparing MEFV-curves when breathing air on the one hand and when breathing a mixture of helium 80% and oxygen 20% ("heliox") on the other hand. Helium has an approximately 65% lower density and a 12% higher viscosity than air (Schilder et al, 1963; Bogaard et al, 1982).

Several authors (Despas et al, 1972; Dosman et al, 1975; Ingram and McFadden, 1977) have used the equal pressure point concept (EPP) of Mead et al (1967) to explain the phenomenon of density dependence. Normally EPP is located in the large airways which have a small combined cross sectional area. Here, airflow is mostly determined by convective acceleration and turbulence with high Reynolds numbers. When breathing a gas with a lower density like heliox, Reynolds numbers will be lowered and flow becomes more laminar which results in a higher flow rate. This appears to be the case in normal subjects and in patients with an obstruction in the larger airways. However, in patients whose airflow resistance is mainly located in small peripheral airways, the EPP has moved upstream to the periphery of the lung, where the total cross sectional area of the airways is large and Reynolds numbers are low resulting in an airflow pattern which is mainly laminar. Now, breathing a gas with a low density will not influence the flow pattern and density dependence will not occur or be low. Two examples of MEFV-curves breathing heliox superimposed on MEFV-curves breathing air are shown in Figure 5.

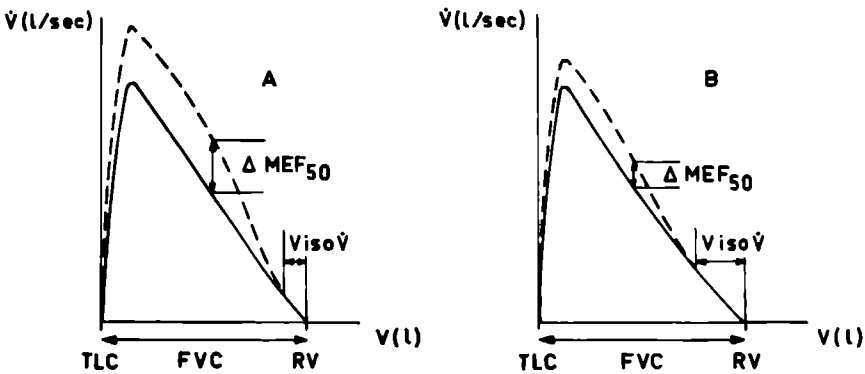

Figure 5 Two examples of MEFV-curves breathing air (—) and a helium oxygen mixture (---).
A represents a positive density dependence ("responder"): MEF_{50} >20% and $V_{iso}\dot{V}$ >80% of the FVC.
B represents a low density dependence ("non-responder"): MEF_{50} <20% and $V_{iso}\dot{V}$ <80% of the FVC.

The parameters derived from this combined curve are:

1. the increase in MEF_{50} after heliox as compared to MEF_{50} breathing air.
2. the volume of isoflow.

Ad 1) The increase in MEF_{50} after heliox (MEF_{50} HeO_2) in comparison with the MEF_{50} breathing air (MEF_{50} air) is usually expressed as

the ratio $\frac{MEF_{50}\ HeO_2 - MEF_{50}\ air}{MEF_{50}\ air} \times 100\% = \Delta MEF_{50}$.

According to Despas et al (1972) an increase in ΔMEF_{50} of more than 20% is called a positive density dependence. They, and later on Dosman et al (1975), discovered that normal subjects and some patients with CNSLD had a ΔMEF_{50} of more than 20% and they are called "responders", while other patients with CNSLD or smokers had a lower ΔMEF_{50} and therefore are called "non-responders". ΔMEF_{25}, being the increase in MEF_{25} after breathing heliox is less frequently used.

Ad 2) The volume isoflow ($V_{iso}\ \dot{V}$): this is the lung volume at which respiratory flow is the same with air as with the heliox mixture (Hutcheon et al, 1974; Dosman et al, 1975). During this part of the MEFV-curve airflow is independent of the density and viscosity of the respired gas. $V_{iso}\ \dot{V}$ is usually expressed as a percentage of the FVC ($V_{iso}\ \dot{V}$/FVC).

Both parameters have been used a) to detect early changes in peripheral airways dysfunction as caused by smoking in comparison with non-smokers (Hutcheon et al, 1974; Dosman et al, 1975; Gelb et al, 1975); b) to compare asthmatics with patients with irreversible airways obstruction (Despas et al, 1972) and c) to study the effects of bronchoconstrictor and bronchodilator agents on large and small airways function (Chan-Yeung, 1976; Chick and Jenne, 1977; Brown et al, 1977; Douglas et al, 1979; Ashutosh et al, 1980; Minette et al, 1985).

The effects of constrictor and dilator stimuli on central or more peripheral airways can be differentiated by means of the density de-

pendence (ΔMEF_{50}) as shown in the following diagram (Ingram and McFadden, 1977; Ashutosh et al, 1980; Minette et al, 1985).

When bronchoconstriction is mostly located in small airways ΔMEF_{50} will be low, whereas ΔMEF_{50} will be higher when the airflow limitation is situated in larger airways.

	ΔMEF_{50} ↓	ΔMEF_{50} ↑
Bronchoconstriction	peripheral airways > central airways	central airways > peripheral airways
Bronchodilatation	central airways > peripheral airways	peripheral airways > central airways

When ΔMEF_{50} is lower after than before administration of a bronchodilator agent, it means that central airways are dilated and there is still an increased resistance in the peripheral airways. Conversely, this can be said when ΔMEF_{50} rises after bronchodilatation.

Proportionately equal dilatation of central and peripheral airways is thought to be associated with an increase in expiratory flow parameters like FEV_1, MEF_{50} and MEF_{25}, but no change in ΔMEF_{50} (Ingram et al, 1977).

3.4.5. The reproducibility of the MEFV-curve

With regard to the reproducibility of the different parameters which can be assessed from the MEFV curve, a distinction should be made between intersubject and intrasubject variability. According to Quanjer (1983) the variation coefficient of the intersubject variability approximates 30%, while for the intrasubject variability he mentions a coefficient of variation of 5%. Other authors have described a higher within-subject variability (McCarthy et al, 1975; Becklake and Permutt,

1979). FEV_1 and FVC are the most reproducible parameters of the MEFV-curve; PEFR and MEF_{50} are less repeatable, but more than MEF_{25}. Looking at intrasubject variability in our own studies of parameters of MEFV-curves during breathing air or heliox, we found coefficients of variation which are compatible with those cited in literature (Fig. 2).

As the second part of the MEFV-curve is supposed to be effort-independent, it should be more reproducible than the first, effort-dependent phase (Fig 4). This is, however, not true (Fig 2); several sources of variability have been mentioned to explain the greater variability in MEF_{50} and MEF_{25} (Clement and Van de Woestijne, 1971):

- failure to achieve maximum flows early in expiration;
- problems with reaching the same maximum inspiratory level;
- oscillations of maximum flows;
- some degree of effort-dependency of the second phase.

With respect to the reproducibility of the phenomenon of density dependence, it can be concluded from the literature, that while MEF_{50} measurements when breathing normal air and MEF_{50} when breathing heliox appear to be fairly reproducible, the variability of the relationship between these two parameters expressed as density dependence (ΔMEF_{50}) is large, as would be expected on mathematical grounds (Bonsignore et al, 1980; Mac Donald and Cole, 1980).

Berend et al (1981) found a within-subject coefficient of variation for $V_{iso}\dot{V}$ of 65.2% in 10 healthy non-smoking volunteers, who were studied on three consecutive days and on a day one month later.

For this last parameter the inter-observer variability was also higher than for MEF_{50} and ΔMEF_{50}. The reproducibility of ΔMEF_{50} can be enhanced by matching MEFV-curves at TLC level instead of RV level (Johansen and Vale, 1984).

However, from our own data, as summarized in Figure 2, it appears that the variability of parameters of the MEFV-curve is acceptable, when these curves are used to compare ventilatory effects of pharmacological agents in patients with CNSLD, but only if each patient serves as his own control.

A good repeatability of the maximal airflow at large and low lung volumes is important, because assessment of MEFV-curves is an easy performed method to detect calibre changes in central and peripheral airways.

3.4.6. The partial flow-volume curve

The maximal inspiratory manoeuvre preceding the maximal expiration to obtain a MEFV-curve can influence bronchomotor tone as has been mentioned in paragraph 3.2.3. In order to abolish the bronchodilator or constrictor effects of a maximal inspiratory manoeuvre, partial expiratory flow-volume curves (PEFV-curves) have been proposed to study the airway responses to pharmacological agents and in other bronchial challenge tests (Bouhuys et al, 1969; Barnes et al, 1981; Zamel,1984). This method is suitable to study effects on small airways, especially in normal subjects or patients with mild asthma (Barnes et al, 1981). Barnes and coworkers (1981) demonstrated that in normal subjects PEFV-curves show greater responses than MEFV-curves and that these PEFV-curves were relatively good reproducible within each individual with coefficients of variation of 3 to 12%. In asthmatic patients, however, PEFV-curves appear to offer no advantage over MEFV-curves for the detection of responses to bronchodilators such as β_2-adrenoceptor agonists (Berry and Fairshter, 1985).

3.5. CONCLUSIONS

With regard to the assessment of the effects of β-adrenoceptor agonists and antagonists it is not easy to determine which "test is best". In many lung function laboratories the choice is to a certain extent determined by the presence of measurement facilities. Measurement of airway resistance with the plethysmographic method or by the forced oscillation technique has the advantage of being easy for both investigator and patient. These methods are, however, extremely sensitive and do not discriminate between extra- and intrathoracic airways or effects on large or small airways. Measurement of forced expiratory airflow is the most often used method, either by spirometry or by flow-volume curves. Assessment of FEV_1 is probably the most reproducible and most specific parameter, though not the most sensitive. Nevertheless, the FEV_1 can be regarded as the gold standard for measurement of ventilatory responses of pharmacological agents in patients with

CNSLD. PEFR measurement has the great advantage of the simplicity of the apparatus, the effort dependence and false high readings due to airway compression are, however, disadvantages. Flow-volume curves have the great advantage that from one expiratory manoeuvre several lung function parameters can be obtained. Also a distinction between effects of drugs on large or small airways function can probably be derived from the flow-volume curve. Density dependence of airflow is increasingly used to discriminate between large and small airways function. The large inter- and intrasubject variability of this expiratory flow parameter, however, remains problematical.

Changes in lung function due to the administration of β-adrenoceptor agonists or -antagonists are usually assumed to reflect changes in airway smooth muscles. As these drugs do not only have an effect on the β-adrenoceptor of the smooth muscles, it should be realised that changes in airway calibre can also be caused by effects of these drugs on other β-adrenoceptor containing cells in the airways or by reflex mechanisms, as is described in Chapter 2. In-vitro functional studies and receptor binding studies elucidate the mechanisms of β-adrenoceptor function more basically, lung function measurements, however, remain, for the time being, the only practical method for assessing β-adrenoceptor function of the airways in living man.

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CHAPTER 4

VENTILATORY EFFECTS OF BETA$_1$-RECEPTOR-SELECTIVE BLOCKADE WITH BISOPROLOL AND METOPROLOL IN ASTHMATIC PATIENTS

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SUMMARY

In a double blind, placebo-controlled study the ventilatory effects of the β_1-selective receptor blockers bisoprolol (EMD 33512) and metoprolol and their interactions with the β_2-adrenoceptor agonist terbutaline were investigated in 8 asthmatic patients. Both β-blockers, in all the doses given, caused a significant decrease in peak expiratory flow rate (PEFR). Vital capacity (VC) and forced expiratory volume in one second (FEV_1) were significantly decreased only after 10 mg bisoprolol. Terbutaline inhalation caused the same significant improvements in FEV_1 and PEFR during placebo as during bisoprolol 10 mg, bisoprolol 20 mg and metoprolol 100 mg. both β-blockers caused equal changes in heart rate (HR) at rest. Systolic and diastolic blood pressure (BP) decreased significantly after bisoprolol 20 mg and metoprolol 100 mg, but not after bisoprolol 10 mg. Inhalation of terbutaline up to a dose of 3.5 mg had no influence on HR and BP. The results point to good β_1-selectivity of bisoprolol 10 mg and 20 mg and metoprolol 100 mg in asthmatic patients. No correlation was found between the plasma levels of the β-blockers and the changes in the ventilatory indices, HR or BP.

Keywords: asthma, β_1-selective blockers, bisoprolol, metoprolol; terbutaline inhalation, ventilatory effects, plasma levels.

INTRODUCTION

A well-known side effect of β-receptor antagonists is an increase in bronchospasm in asthmatic patients. Since the introduction of β_1-selective receptor blockers this problem has become less serious, not only because their influence on lung function is limited, but also because the bronchodilator effects of β_2-receptor agonists are not inhibited (Johnsson et al, 1975a; Greefhorst and Van Herwaarden, 1982).

It has been shown in animal experiments and in studies on human volunteers that the recently developed β-receptor blocker bisoprolol has a high degree of β_1-receptor selectivity (Manalan et al, 1981; Leopold et al, 1982). The aim of the present study was to assess the β_1-receptor selectivity of bisoprolol in comparison with metoprolol and placebo by investigating the effects of these drugs on lung function in asthmatic patients. Interaction with the bronchodilator effect of a β_2-receptor agonist was also studied. Since the β_1-receptor selectivity of a β-blocker can diminish in higher dosages, 2 different dose levels of bisoprolol were administered.

PATIENTS AND METHODS

The study comprised 8 male patients with bronchial asthma, defined as paroxysmal, reversible, generalised, airway obstruction. Three of these patients also suffered from chronic bronchitis, with complaints of coughing and sputum expectoration. Clinical details of the patients are listed in Table 1 (next page); their mean age was 39 yrs, mean height 173 cm and mean weight 74.9 kg. Four patients had atopic extrinsic asthma with one of more positive skin tests. All patients were in a stable respiratory state, which means that there had been no respiratory infection or increase in bronchoconstriction within the 4 weeks before the study. Direct bronchodilators, such as theophylline and β_2-receptor stimulating drugs, were discontinued at least 4 days prior the the study; 3 patients continued using disodium cromoglycate without changing the dose during the study period. The mean forced expiratory volume in one second (FEV_1) was 2.34 1, i.e. 50% or more of

Table 1. Patient characteristics.

Subject	Age (years)	Asthma type*	Height (cm)	Weight (kg)	FEV_1			treatment for COLD**
					Actual (L)	% of predicted values	% increase with terbutaline	
1	31	E	185	70.0	2.80	61	35	C Th
2	43	I + CBr	161	73.0	1.55	50	22	F Th
3	49	I + CBr	166	79.0	2.00	63	20	-
4	24	E	175	62.5	2.90	67	19	-
5	40	E	178	93.0	2.50	63	36	C
6	52	I + CBr	172	77.3	1.85	55	24	-
7	36	I	176	88.1	3.10	77	19	S
8	35	E	169	56.2	2.00	54	45	C
mean±SEM	39±3		173±3	74.9±4.3	2.34±0.20			

* E = Extrinsic I = intrinsic CBr = chronic bronchitis

**C = disodium cromoglycate Th = theophylline derivatives, F = fenoterol, S = salbutamol

the predicted normal value (Quanjer 1983), and in all patients the FEV_1 increased more than 15% after stimulation with the β_2-receptor agonist terbutaline (Table 1).

Patients with cardiovascular diseases other than arterial hypertension were excluded from the study. All the patients gave their written informed consent to it. The design of the study was approved by the Ethical Committee of the Medical Faculty of the University of Nymegen.

The investigations were performed on 4 different days, separated by intervals of at least 2 days to serve as washout periods. Placebo was given single blind on the first day. On the following days the patients received, double blind and in random order, bisoprolol 10 mg, bisoprolol 20 mg or metoprolol 100 mg. All measurements started at 11.30 h in order to minimize variation in baseline lung function and to avoid the morning dip, which frequently occurs in asthmatic patients (Connolly 1979). The β-blockers were administered orally before a standard meal to avoid differences in bioavailability within each individual (Melander 1977). Before and 120 min after intake of the medication the following indices were measured: FEV_1, inspiratory vital capacity (VC; Godart Pulmotest, highest of three readings) and PEFR (Wrightpeak flow meter, highest of two readings); the HR was recorded with an electrocardiograph (Hellige); and the BP was assessed with the automatic blood pressure device Physiometrics SR2. Next, a dose-response curve with the β_2-receptor agonist terbutaline was determined by measuring the ventilatory indices, HR and BP, 15 min after inhalation of increasing dosages. Terbutaline was inhaled from a metered dose aerosol, each puff containing 0.5 mg terbutaline sulphate (Draco, Sweden), in cumulative dosages of 0.5 mg,1.5 mg and 3.5 mg. At 2 h and 3 h 15 min after drug intake, a blood sample was collected for determination of the plasma levels of the β-blockers. The plasma levels were measured by HPLC (E. Merck, Darmstadt, FRG), in samples stored at -20°C until analyzed.

All results are presented as mean $\pm$ SEM. Statistical analysis was performed with the Wilcoxon test for paired observations. Statistical significance was defined as $p<0.05$.

There were no significant differences in ventilatory indices, HR and BP, measured before drug intake on the 4 study days. The changes in ventilatory indices 2 h after intake of the tablets are presented in Table 2 (next page) and Fig. 1.

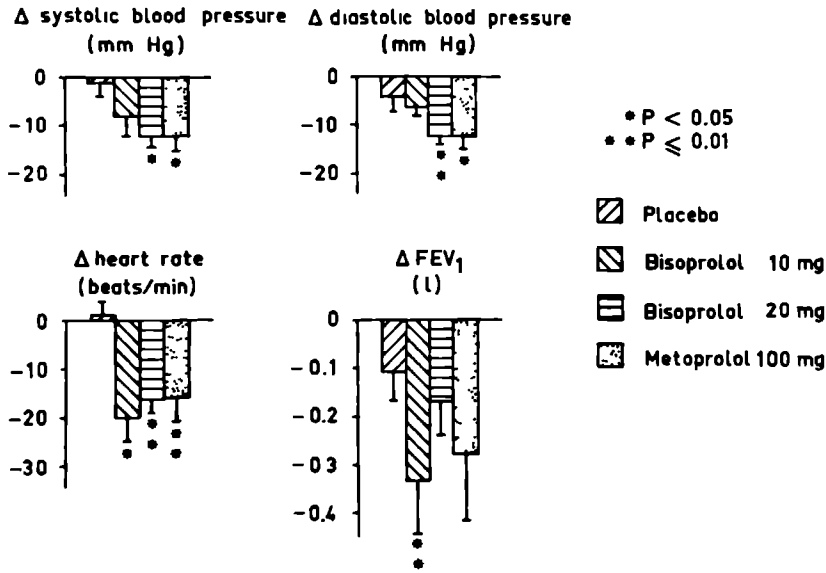

Figure 1. Changes in blood pressure, heart rate and FEV_1 2 h after intake of placebo, bisoprolol 10 mg and 20 mg, and metoprolol 100 mg (mean ± SEM; n=8).

Both β-blockers caused a significant decrease in PEFR. The decrease in FEV_1 was significant at the 1% level for bisoprolol 10 mg, but not for bisoprolol 20 mg or metoprolol 100 mg. The VC decreased significantly only after bisoprolol 10 mg. There were no significant differences between the changes in ventilatory indices induced by these β-blocking agents 2 h after drug intake.

Table 2. Ventilatory indices before and after ingestion of placebo, bisoprolol and metoprolol and after inhalation of cumulative doses of terbutaline (mean±SEM; n=8).

	initial value	2 hours after drug intake	p*	terbutaline 0.5 mg	p**	1.5 mg	p**	3.5 mg	p**
FEV_1 (L)									
placebo	2.33±0.19	2.21±0.18	NS	2.69±0.23	<0.01	2.90±0.25	<0.01	2.96±0.24	<0.01
bisoprolol 10 mg	2.43±0.17	2.10±0.18	<0.01	2.59±0.18	<0.01	2.88±0.24	<0.01	2.98±0.24	<0.01
bisoprolol 20 mg	2.34±0.17	2.18±0.20	NS	2.52±0.17	<0.02	2.81±0.22	<0.01	2.88±0.24	<0.01
metoprolol 100 mg	2.47±0.23	2.20±0.18	NS	2.54±0.22	NS	2.77±0.23	<0.01	2.91±0.25	<0.01
PEFR (L/min)									
placebo	338 ±22	329 ±18	NS	382 ±23	<0.01	403 ±23	<0.01	410 ±20	<0.01
bisoprolol 10 mg	351 ±18	301 ±20	<0.01	376 ±20	<0.01	402 ±23	<0.01	416 ±23	<0.01
bisoprolol 20 mg	348 ±14	298 ±19	<0.02	366 ±12	<0.01	393 ±16	<0.01	405 ±19	<0.01
metoprolol 100 mg	358 ±24	291 ±23	<0.02	362 ±23	<0.01	387 ±28	<0.01	409 ±23	<0.01
VC (L) placebo									
placebo	3.93±0.33	3.86±0.33	NS	4.06±0.31	<0.01	4.13±0.31	<0.01	4.24±0.33	<0.01
bisoprolol 10 mg	4.04±0.27	3.78±0.28	<0.02	4.09±0.31	<0.01	4.19±0.31	<0.01	4.21±0.32	<0.01
bisoprolol 20 mg	3.99±0.31	3.88±0.31	NS	4.03±0.29	NS	4.19±0.33	<0.05	4.13±0.32	NS
metoprolol 100 mg	4.09±0.33	3.88±0.28	NS	4.09±0.29	<0.05	4.13±0.28	<0.02	4.24±0.31	<0.01

p* p-value 2 h after drug intake versus initial value
p** p-value versus 2 h after drug intake
NS not significant

Inhalation of terbutaline in increasing doses led to significant stepwise improvements in FEV_1 and PEFR (Table 2 [page 69], Fig. 2 [page 71]). The effect of terbutaline on the indices was of the same magnitude after bisoprolol 10 mg and 20 mg and metoprolol as after placebo. The improvements in VC were less pronounced (Table 2).

Both β-blocking agents caused a significant decrease in HR 2 h after administration (Fig. 1). The systolic and diastolic BP declined significantly after intake of bisoprolol 20 mg and metoprolol 100 mg, whereas the decrease after bisoprolol 10 mg was not significant. No change in these values after placebo was observed. Inhalation of terbutaline had no influence on HR and BP (Fig. 3) (page 72).

The plasma levels of the β-blockers are presented in Table 3. The plasma levels of bisoprolol 10 mg and bisoprolol 20 mg remained constant between 120 and 195 min after drug intake. The plasma metoprolol level, however, decreased significantly over that period.

Table 3. Plasma level of bisoprolol after 10 and 20 mg doses and of metoprolol after 100 mg (ng/ml) 2 h and 3 h 15 min after drug intake (mean ± SEM; n=8).

	bisoprolol 10 mg	bisoprolol 20 mg	metoprolol 100 mg
120 min	45 ± 6	83 ± 6	78 ± 15
range	15 - 65	62 -107	34 -155
195 min	42 ± 4	80 ± 5	54 ± 19
range	25 - 66	67 -110	21 - 96
120 min versus 195 min	NS	NS	$p < 0.05$

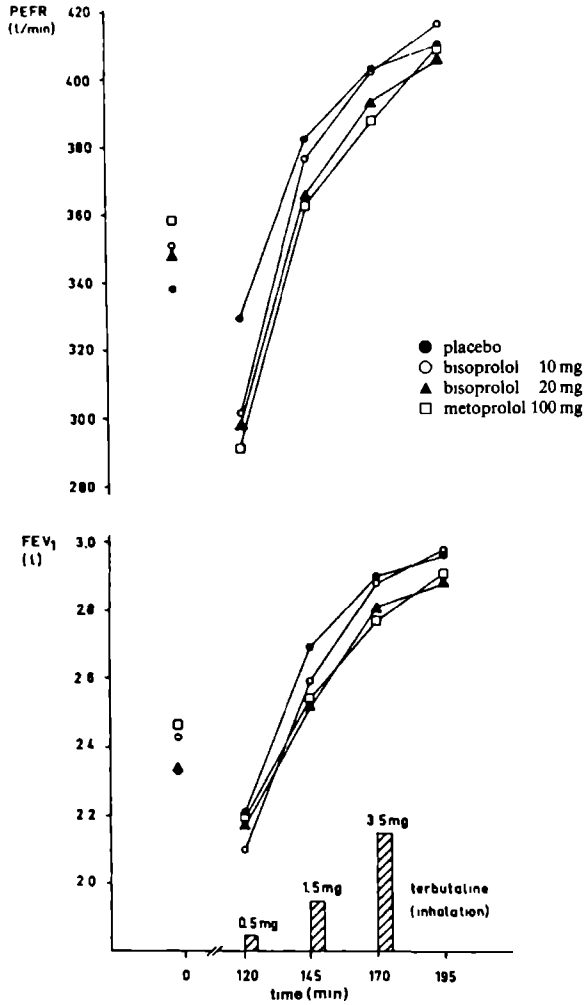

Fig. 2 Changes in FEV_1 and PEFR induced by inhalation of terbutaline in cumulative doses after placebo, bisoprolol 10 mg and 20 mg, and metoprolol 100 mg.

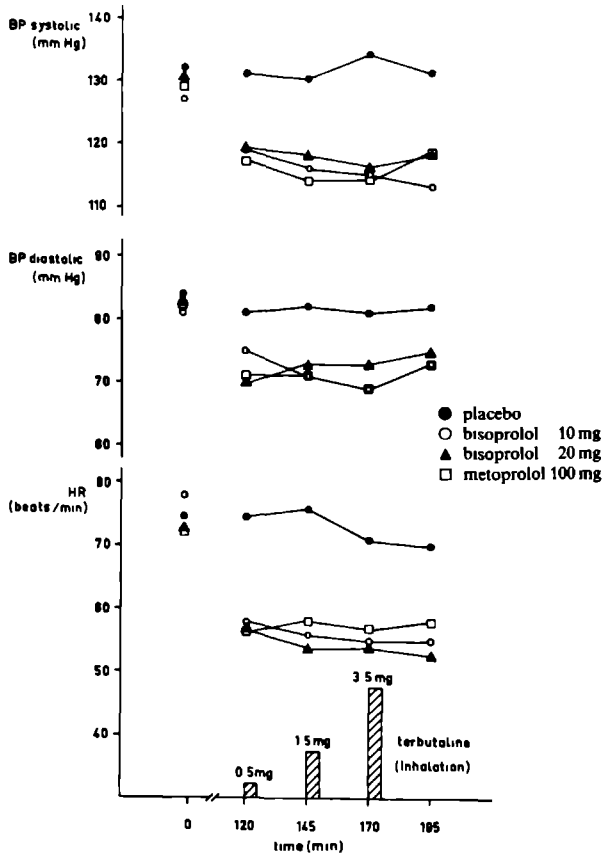

Fig. 3 Effect of inhalation of terbutaline in cumulative doses on blood pressure and heart rate after placebo, bisoprolol 10 mg and 20 mg, and metoprolol 100 mg.

DISCUSSION

The study was performed in asthmatic patients with an increase in FEV_1 of more than 15% after administration of terbutaline. It was necessary to study patients with this type of reversible airway obstruction, because in asthmatic patients with low reversibility β-blockers have no appreciable effect on airway obstruction. The latter type of patient is unsuitable for study of the β_1-receptor selectivity of β-blockers (Nordström et al, 1975; Perks et al, 1978).

It has been demonstrated that metoprolol caused bronchoconstriction in asthmatic patients, which is completely reversible with a β_2-receptor agonist, indicating the β_1-receptor selective character of metoprolol (Johnsson et al, 1975a; Greefhorst and Van Herwaarden, 1982). Animal studies and work in healthy human volunteers have shown that bisoprolol is a β-receptor antagonist with a high degree of β_1-receptor selectivity and, like metoprolol, it lacks partial agonist activity (Manalan et al, 1981; Leopold et al, 1982). As bisoprolol 10 mg and metoprolol 100 mg are equivalent in terms of their effect in reducing exercise-induced tachycardia (Leopold et al, 1982), the effect of these doses was compared. A study was also made of whether the effect of bisoprolol was enhanced when the dose was raised to 20 mg, because it is known that at higher dosages β_1- receptor-selective antagonists can also block β_2-receptors (Lertora et al, 1975).

In the present study bisoprolol 10 mg and 20 mg and metoprolol 100 mg caused the same significant reduction in HR at rest. BP decreased significantly after bisoprolol 20 mg and metoprolol 100 mg (Fig. 1). Inhalation of the β_2-receptor selective agonist terbutaline had no effect on HR and BP.

Both β-receptor blockers caused an increase in bronchoconstriction, as shown by a decrease in PEFR. It was not possible to demonstrate a dose-related effect of bisoprolol on lung function.

The improvement in lung function after inhalation of terbutaline was similar for bisoprolol, metoprolol and placebo (Fig. 2). The dose response curve for a β_2-receptor agonist in patients on β-receptor blockade gives information on the degree of selectivity of the β-receptor blocker. During nonselective β-receptor blockade, the curve

shifts to the right as compared with a β_1- receptor selective blocker and placebo, as a consequence of blockade of β_2- receptors in the airways (Johnsson et al, 1975a; Greefhorst and Van Herwaarden, 1982). The results indicate similar β_1-receptor selectivity for bisoprolol and metoprolol, because the positions of the dose-response curves were the same after both β-receptor blockers.

The effects on lung function of these β_1-receptor selective antagonists can be explained in two ways: the β-blockers are not completely β_1-receptor-selective, or the airways also contain functional β_1-adrenoceptors. Further studies are needed to solve this question.

Plasma levels after bisoprolol 20 mg were twice as high as those after bisoprolol 10 mg, which is in accordance with the doses administered and the known pharmacokinetics of this drug (Leopold et al, 1982). There was only a minor change in plasma bisoprolol level between 2 h and 3 h 15 min after drug intake, whereas the plasma level of metoprolol decreased significantly over the same period (Table 3). The difference can be explained by the half-lives of the β-blockers, namely 11 and 3 h for bisoprolol and metoprolol, respectively (Johnsson et al, 1975b; Leopold et al, 1982). No correlation was found between the plasma levels of the β-blockers and their effects on the ventilatory indices, HR and BP.

Acknowledgement

Bisoprolol was kindly provided by E. Merck, Darmstadt, where the plasma level determinations were also performed by HPLC.

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CHAPTER 5

VENTILATORY EFFECTS OF LONG-TERM TREATMENT WITH PINDOLOL AND METOPROLOL IN HYPERTENSIVE PATIENTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASE

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SUMMARY

1. Effects of long-term treatment with pindolol (10 mg twice daily) and metoprolol (100 mg twice daily) on lung function and blood pressure were investigated in eight patients with chronic obstructive lung disease and hypertension.

2. After a placebo period, both β-adrenoceptor blockers were administered double-blind and cross-over for 4 weeks.

3. By assessing parameters of expiratory flow an attempt was made to distinguish between large and small airways function.

4. Diastolic blood pressure decreased significantly during both pindolol and metoprolol ($p<0.01$).

5. Except for a decrease in forced expiratory volume in 1 s (FEV_1) during metoprolol treatment, there was no other change in expiratory flow parameters after placebo or both β-adrenoceptor blockers.

6. Inhalation of terbutaline induced a small improvement in large airways function after placebo and metoprolol, but not after pindolol; there was no effect of terbutaline on parameters of small airways function.

7. If a β-adrenoceptor blocker is necessary in patients with chronic obstructive lung disease, a β_1-adrenoceptor selective blocker is preferred in combination with bronchodilator agents.

Keywords: hypertension, metoprolol, pindolol, chronic obstructive lung disease

INTRODUCTION

β-adrenoceptor antagonists can induce or aggravate bronchoconstriction in patients suffering from chronic obstructive lung disease. The degree of airway obstruction induced by β-adrenoceptor blockers depends on ancillary properties of these drugs. It has been demonstrated that β_1-adrenoceptor selective antagonists such as metoprolol, and β-adrenoceptor blockers with intrinsic sympathomimetic activity such as pindolol, have a less detrimental effect on lung function than nonselective β-adrenoceptor blockers such as propranolol (Johnsson et al., 1975; Ulmer et al., 1976; Ruffin et al., 1982).

Moreover, the bronchodilator response to a β_2-adrenoceptor agonist is blocked by a nonselective β-adrenoceptor blocker, but not by a β_1-adrenoceptor selective blocker (Benson et al., 1978).

The untoward ventilatory effects of β-adrenoceptor blockers in patients with asthma or chronic obstructive bronchitis are hardly predictable, but patients with a low-reversible or fixed bronchial obstruction generally show no deterioration of lung function during β-adrenoceptor blockade (Perks et al., 1978).

Most of the above conclusions were based on short-term studies. The purpose of this investigation was to determine the ventilatory effects of metoprolol and pindolol during long-term treatment in a group of hypertensive patients with chronic obstructive lung disease, while they continued bronchodilator therapy.

METHODS

Eight patients, seven males and one female, with chronic obstructive lung disease and hypertension completed the study. Some clinical details of the patients are listed in Table 1 (next page). Seven patients suffered from chronic bronchitis, while patient number 7 was an asthmatic with several positive skin tests and a low histamine tolerance during provocation. These diagnoses were made in accordance with the diagnostic standards of the American Thoracic Society (1962). There were no patients with emphysema. During bronchodilator therapy the forced expi-

Table 1 Patient characteristics.

Subject	Age (y)	Height (cm)	Weight (kg)	TLC* (L)	FVC* (L)	FEV_1(L)* before terbutaline	FEV_1(L)* after terbutaline	MEF_{50}* (Ls^{-1})	Treatment** for chronic obstructive lung disease
1	44	161	77	5.8(103)	3.0(79)	2.2(71)	2.2	2.3(52)	B F Th
2	52	177	90	6.7(94)	4.7(104)	3.6(97)	3.8	3.5(74)	B S Th
3	59	158	71	4.9(106)	1.7(65)	0.7(31)	1.1	0.4(11)	S Th
4	60	179	75	7.0(95)	3.3(75)	1.9(53)	2.1	1.0(22)	S Th
5	62	179	95	8.4(114)	2.7(61)	1.1(31)	1.4	0.4(8)	B S Th
6	49	177	96	5.9(83)	4.2(91)	3.1(79)	3.2	3.5(73)	S
7	35	185	82	7.9(100)	5.3(98)	4.2(89)	4.7	4.0(71)	C S
8	60	172	83	7.0(106)	3.8(95)	2.2(66)	2.2	1.4(33)	B S
mean	52.7	173.5	83.6	6.70	3.58	1.93	2.59	2.06	
± SEM	0.4	3.3	3.3	0.41	0.41	0.42	0.43	0.52	

* values in parentheses: % of predicted normal values (Quanjer, 1983).

** B = beclomethasone; C = cromoglycate; F = fenoterol; S = salbutamol; Th = long-acting theophylline

TLC = total lung capacity measured by helium dilution
FVC = forced vital capacity (L)
FEV_1 = forced expiratory volume in one second (L)
MEF_{50}= maximal expiratory flow rate at 50% of FVC (Ls^{-1})

ratory volume in 1 s (FEV_1) improved > 10% in four patients and remained almost unchanged in the other four patients (Table 1). All patients were in a stable respiratory state which means that they had had no respiratory infection or increase in bronchoconstriction during the last month before the study. They continued the medication for their chronic obstructive lung disease during the study period in the same doses as before the study (Table 1). They were only allowed to increase the amount of the inhaled β_2-adrenoceptor agonist, which event had to be recorded on a symptom diary card.

Hypertension was defined as a diastolic blood pressure $\geq$ 95 mm Hg (measured on three occasions; Korotkoff phase 5). One patient was accepted with a diastolic blood pressure of 90 mm Hg, while taking a diuretic. Patients with cardiovascular diseases other than arterial hypertension were excluded from the study. The study was approved by the local Ethics Committee and written informed consent was obtained from each patient. The study was designed as a placebo controlled, double-blind cross-over comparison between pindolol and metoprolol. All patients were in the trial for 12 weeks. During the first 4 weeks they ingested single-blind a placebo twice a day. Next, they received double-blind and cross-over, pindolol 10 mg twice daily or metoprolol 100 mg twice daily, each during 4 weeks.

The patients were examined at the out-patient clinic at 2 week intervals. At every visit blood pressure (BP) and heart rate (HR) were assessed. After 15 min of rest BP was measured in the supine (two readings) and the erect position with a Hawksley random zero sphygmomanometer. Before the study and after each 4 week period lung function was measured with flow-volume equipment (Pneumoscreen No. II, Jaeger). Flow-volume curves were plotted on an X-Y recorder (Hewlett Packard 7045B). Several components of airflow rate and exhaled lung volume were assessed with the so-called envelope method: the indices were read on the composite curve, obtained by taking the envelope of three individual curves superimposed at TLC level (Peslin et al., 1979). FEV_1, forced vital capacity (FVC) and peak expiratory flow rate (PEFR) give predominantly information on the air flow in the larger airways; the maximal expiratory flow rates at 50% and especially at 25% of the FVC (MEF_{50} and MEF_{25} respectively) are thought to be indicators that are

more specific of smaller airway conductance 1979). On the morning of the lung function measurements the patients did not take β_2-adrenoceptor agonists.

Under this "baseline" condition lung function was assessed for each patient at a fixed time of the day in order to minimize diurnal variation in lung function (Connolly, 1979). Lung function measurements were repeated after inhalation of the β_2-adrenoceptor agonist terbutaline. Terbutaline was inhaled with a metered dose aerosol in cumulative dosages of 1.0 mg and 2.0 mg. Symptom diary cards which recorded diurnal dyspnoea, dyspnoea at night, sleep disturbances and medication were completed daily by each patient. Before inhalation of bronchodilator medication, PEFR was recorded twice a day with a Wright mini peak flow meter (highest value of three readings). Statistical analysis was performed with the Wilcoxon test for paired observations. Statistical significance was defined as $p<0.05$ (Colton, 1974).

RESULTS

In comparison with the values during placebo, diastolic BP declined significantly during treatment with both pindolol and metoprolol (Table 2) (next page). There were no statistically significant differences between the effects on BP of pindolol and metoprolol. HR decreased significantly during treatment with both β-adrenoceptor blockers; there was no significant difference between the heart rate during pindolol and that during metoprolol (Table 2).

The daily measured PEFR remained constant throughout the study: there were no statistically significant differences between the values during placebo and those during both β-adrenoceptor blockers (Table 3) (next page). The PEFR did not change during the day: the morning and evening values were the same throughout the study. Statistical analysis of the data obtained from the symptom diary cards did not show any differences in the pulmonary complaints of the patients between any of the three study periods, nor was there any change in the amount of bronchodilator medication used. The effect of placebo and both β-adrenoceptor blockers on the ventilatory indices measured after each 4

Table 2 Blood pressure and heart rate at rest after 4 weeks on placebo and 4 weeks of β-adrenoceptor blockade (mean ± s.e. mean, n=8).

	PLACEBO	PINDOLOL	p*	METOPROLOL	p**	p***
Systolic pressure (mm Hg)						
supine	148±5	135±6	NS	134±3	<0.01	NS
erect	145±4	135±6	NS	124±4	<0.01	NS
Diastolic pressure (mm Hg)						
supine	102±3	91±3	<0.01	89±3	<0.01	NS
erect	107±4	92±4	<0.01	90±3	<0.01	NS
Heart rate (beats min^{-1})	78±4	66±2	<0.05	62±2	<0.01	NS

p* pindolol versus placebo. p** metoprolol versus placebo. p*** pindolol versus metoprolol. NS not significant

Table 3 Daily measured PEFR (L min^{-1}) after 4 weeks on placebo and 4 weeks of β-adrenoceptor blockade (mean ± s.e. mean, n=8).

	Morning	Evening
placebo	377±53	378±48
pindolol	360±55	357±55
metoprolol	370±55	371±51

week period are shown in Figures 1 and 2. The baseline FEV_1 during metoprolol was significantly lower than that during placebo ($p < 0.05$), but did not differ from the baseline FEV_1 during pindolol (Figure 1).

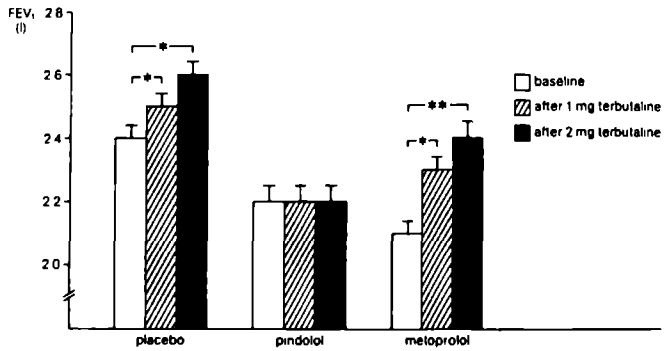

Figure 1. Effects of placebo and β-adrenoceptor blockade and stimulation with terbutaline on FEV_1 (L), mean ± s.e.mean, n=8. *p<0.05, **p<0.01.

There were no statistically significant differences between the baseline values of the FVC and PEFR (Figure 2) and of the MEF_{50} and MEF_{25} during placebo and both β-adrenoceptor blockers.

Inhalation of terbutaline up to a cumulative dose of 2 mg induced a small, but significant increase in FEV_1, FVC and PEFR during placebo and metoprolol, but not during pindolol (Figures 1 and 2). The MEF_{50} and MEF_{25} values did not change after inhalation of terbutaline during placebo or both β-adrenoceptor blocking agents.

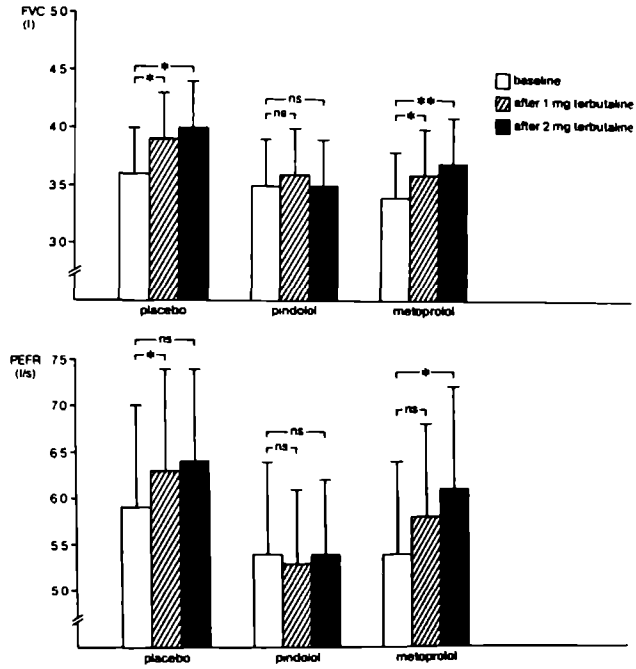

Figure 2. Effects of placebo and β-adrenoceptor blockade and stimulation with terbutaline on FVC (L) and PEFR (Ls^{-1}), mean ± s.e.mean, n=8. *p<0.05, **p<0.01.

DISCUSSION

BP and HR at rest were effectively lowered by both pindolol and metoprolol in this group of hypertensive patients with chronic obstructive lung disease. Daily measurements of PEFR is actually the only practical method to assess the lung function of patients at hom (Pride, 1979). In our patients the daily measured PEFR remained unchanged during the placebo period and during treatment with both β-adrenoceptor blockers. We could not demonstrate a difference between morning and evening PEFR values. All patients were in a stable respiratory state before they entered the study and remained so throughout the study period. The baseline lung function measurements assessed during the

clinical visits, demonstrated a small decrease in FEV_1 during metoprolol, but not during pindolol treatment. The partial agonist activity of pindolol probably caused some stimulation of the bronchial β-adrenoceptors under baseline conditions. The bronchodilator response to terbutaline was completely inhibited by pindolol, but not affected by metoprolol. This difference is in accordance with the β_1-adrenoceptor-selective property of metoprolol and the nonselective character of pindolol (Johnsson et al., 1975; Benson et al., 1978).

This bronchodilation, however, could only be assessed by increases in FEV_1, FVC and PEFR. There was no change in MEF_{50} and MEF_{25} either during β-adrenoceptor blockade or during β-adrenoceptor stimulation. In this group of patients with chronic obstructive lung disease the lumen of the larger airways is at least partially dependent on changes in smooth muscle tone and sensitive to β-adrenoceptor modulation. The airflow in the more peripheral airways, on the other hand, appeared to be insensible to β-adrenoceptor modulation and is possible more dependent on structural changes in the walls of these airways. Patakas et al. (1983) demonstrated a decrease in parameters of small airways function after a single dose of 2.5 mg pindolol in asthmatic patients, while there was no significant effect of pindolol on large airways function. As in our patients, however, Dorow et al. (1980) found no change in parameters of large and small airways function after administration of pindolol to patients with chronic obstructive bronchitis. The difference in effect of pindolol on small airways function between these studies might be explained by a difference in patient selection, i.e. a difference in reversibility of bronchial obstruction. Moreover, our patients continued to use their bronchodilator therapy. Differentiation between the effects of the used β-adrenoceptor blockers on large and small airways function, however, remains difficult, as we have investigated a relatively small group of patients. By measuring maximal expiratory flow breathing air and a helium-oxygen mixture, it might be possible to obtain a better discrimination between the effects of β-adrenoceptor blockers on large and small airways conductance (Bogaard et al., 1982; Despas et al., 1972). In a future study we will try to elucidate this question. Nevertheless, our data show that the lung function in this group of hy-

pertensive patients with chronic obstructive lung disease was virtually not depressed by metoprolol or pindolol at dosages which ensured a good regulation of their hypertension. In comparison with metoprolol, however, pindolol inhibited the bronchodilator response to terbutaline in the larger airways. If long-term treatment with a β-adrenoceptor blocker is necessary in patients with chronic obstructive lung disease, a β_1-adrenoceptor-selective blocker is preferred in combination with bronchodilator agents and under regular control of lung function.

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Chapter 6

VENTILATORY EFFECTS OF ATENOLOL AND BEVANTOLOL IN ASTHMA

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SUMMARY

The cardioequipotency of 400 mg bevantolol and 100 mg atenolol was determined by measuring the exercise heart rate in healthy volunteers. The β-blockers were then used in these doses to investigate their ventilatory effects in patients with asthma.

The effects of both drugs on forced expiratory flow parameters for large and small airways were assessed at rest and during and after exercise. A dose-response curve was then plotted after inhalation of the β_2-adrenoceptor agonist terbutaline. Bevantolol significantly decreased the forced expiratory volume in 1 second (FEV_1) and the peak expiratory flow rate (PEFR) at rest, while there was no such change with placebo or atenolol. Both β-blockers decreased the maximal expiratory flow rated at 50% of forced vital capacity (MEF50) and after expiration of 75% of the forced vital capacity (MEF_{25}) at rest; the decrease was larger after bevantolol than after atenolol. During atenolol there was a decrease in FEV_1 and in PEFR ($p<0.01$) 15 minutes after exercise in comparison with preexercise values. There was no significant difference between pre-and postexercise values of MEF_{50} and MEF_{25} during atenolol dosing. After bevantolol there was only a small change in PEFR after exercise, probably because of the low preexercise values of the ventilatory indices with this drug. Inhalation of terbutaline up to a dose of 2 mg significantly improved all ventilatory indices measured, but with bevantolol the values after 2 mg inhaled terbutaline were lower than the initial values. We conclude that atenolol and bevantolol have different effects on large and small airways function in patients with asthma and that the effect of exercise on bronchoconstriction can be enhanced by β-blockade.

Furthermore, 100 mg atenolol appears to be more β_1-adrenoceptor-selective than 400 mg bevantolol.

INTRODUCTION

Studies of the ventilatory effects of β-adrenoceptor antagonists in patients with asthma and reversible bronchial obstruction have proved

to be good models for assessment of the β_1-adrenoceptor selectivity of these drugs[9,11]. Atenolol has been shown to be a β_1-adrenoceptor selective blocker inducing a limited decrease in airway conductance that can easily be reversed by a β_2-adrenoceptor agonist[6,14]. Bevantolol is a new β-adrenoceptor antagonist with β1-adrenoceptor selective effects in animals[8]. Our aim was to investigate the β_1-adrenoceptor selectivity of bevantolol in comparison with atenolol in patients with asthma. In many studies on the effects of β-blockade on lung function, only parameters of large airways function are measured. We were interested whether the influence of these drugs on large airways function on the one hand and conductance in the more peripheral airways on the other hand would differ.

The effects of β-blockers on lung function in patients with asthma can be enhanced by exercise[15,22,23]. This phenomenon is probably caused by a more effective β-blockade during a state of increased sympathetic tone. We therefore measured lung function at rest and during exercise. To compare cardioequipotent doses of both drugs, we first determined in healthy subjects which dose of bevantolol caused the same reduction in exercise-induced tachycardia as 100 mg atenolol.

METHODS

The study to determine cardioequipotency was carried out in six healthy men 21 to 25 years old. Each subject was studied on 4 days at intervals of at least 1 week; a training effect could thus be discounted. After arrival at the hospital at 9.00 AM, the subjects rested 30 minutes before the first exercise test began. Each exercise test consisted of 5 minutes of bicycling on an electrically braked ergometer at an individually determined load that induced a heart rate of approximately 150 bpm before drug dosing. After the first test the study drugs were taken by mouth. On the first day the subjects took (single-blind) a placebo; on the 3 other days they received (double-blind in random order) 200 mg bevantolol, 400 mg bevantolol, and 100 mg atenolol. Subsequent exercise tests were performed 1, 2, 3, 5 and 7 hours after dosing. At each test the heart rate was recorded by a continuous ECG trac-

ing and blood samples were drawn for determination of the plasma levels of the β-blockers. Samples were stored at -20°C until analyzed by HPLC.

To compare the ventilatory effects of bevantolol and atenolol, we studied eight men with bronchial asthma[1]. Clinical data of these patients are listed in Table I.

TABLE I Patient characteristics

Patient No.	Age (yr)	Asthma type	Height (cm)	Weight (kg)	FEV_1 (L)	% Increase with terbutaline	Therapy
1	36	I	176	85	3.1(74)	16	C
2	21	E	178	61	2.6(55)	29	-
3	20	E	177	62	2.7(57)	56	C
4	20	E	185	73	3.7(71)	24	-
5	35	E	177	73	1.9(45)	21	CBS
6	23	E	171	62	2.3(53)	35	-
7	46	E	164	62	2.7(83)	22	B
8	20	E	180	60	2.4(50)	42	CS
$\bar{X}\pm SE$	27.6±3.5		176±2.2	67.3±3.1	2.68±0.19	30.6±4.7	

Values in parentheses are the percentage of predicted values.[21]

E=extrinsic; I=intrinsic; B=beclomethasone; C=cromoglycate; S=salbutamol.

Seven patients had atopic extrinsic asthma with one or more positive tests. Two patients (nos. 1 and 5) (Table I), were cigarette smokers and the others were nonsmokers. All patients were in a stable respiratory state (no respiratory infection or increase in bronchoconstric-

tion within the past month). Salbutamol was stopped in the two patients who used this drug regularly at least 2 days before the study; four patients continued cromoglycate and two continued beclomethasone therapy without a change in dose during the study. In all patients the FEV_1 increased by >15% after stimulation with the β2-adrenoceptor agonist terbutaline. Patients with cardiovascular diseases other than arterial hypertension were excluded. The study was approved by the local Ethics Committee and informed consent was obtained from each patient.

The study was designed as a placebo-controlled, double-blind, crossover comparison of single doses of 400 mg bevantolol and 100 mg atenolol. Every patient was studied on 3 different days, separated by intervals of at least 2 days as washout periods. All experiments started at noon to minimize variation in baseline lung function and to avoid the "morning dip" that frequently occurs in patients with asthma[3].

The following measurements were determined each day: After a resting period of 30 minutes the patients exercised for 5 minutes on a bicycle ergometer at an individually fixed load that induced a heart rate of approximately 150 bpm after placebo. Heart rate and blood pressure were measured before, during the last minute of exercise, and 15 minutes after exercise. At the same time lung function was assessed with flow-volume equipment. Several components of air flow rate were recorded: FEV_1 and PEFR as parameters of large airways function, and MEF_{50} and MEF_{25} mainly as parameters of smaller airways conductance[20]. These indices were obtained from the curve yielding the largest sum of FVC and FEV_1[5,19]. Immediately after this first exercise test the medication was taken by mouth 30 minutes before a standard meal to avoid differences in bioavailability within each individual[16]. Two hours after dosing a second exercise test was performed, which consisted of 5 minutes bicycling at the same load as during the first exercise test. The same measurements were assessed before, during the last minute of exercise, and 15 minutes after exercise. Twenty-five minutes after this second exercise period (i.e., 2.5 hours after drug dosing) a dose-response curve was constructed by measuring the forced expiration indices, heart rate, and blood pressure 15 minutes after

terbutaline inhalation. Terbutaline was inhaled three times from a metered dose aerosol, each puff containing 0.5 mg terbutaline sulphate in cumulative doses of 0.5, 1 and 2 mg.

Statistical analysis was performed by the Wilcoxon test for paired observations and correlations were calculated by the Pearson method[2]. Statistical significance was defined as $p<0.05$.

RESULTS

Study in healthy subjects.

Both β-blockers induced significant decreases in exercise-induced tachycardia in comparison with placebo ($p<0.01$). The largest reduction in exercise-induced tachycardia was measured 2 hours after drug dosing, at which time the effects of 400 mg bevantolol and 100 mg atenolol were identical (-37 bpm) and greater than that of 200 mg bevantolol (-34 bpm). The curves of the plasma concentrations of the β-blockers are shown in Fig. 1.

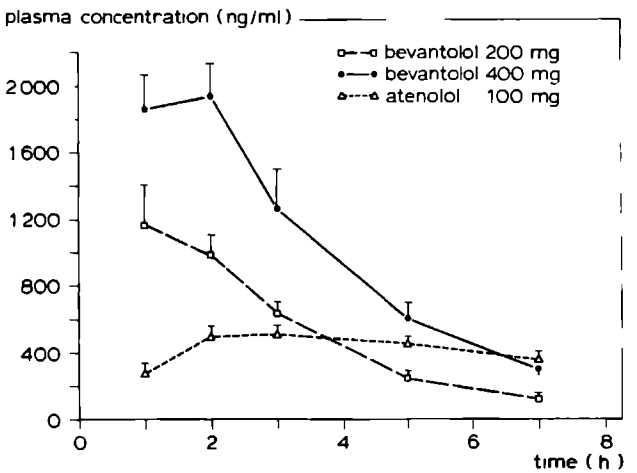

Fig. 1. Mean (±SE; n=6) plasma concentration after oral dosing with 200 mg bevantolol, 400 mg bevantolol, and 100 mg atenolol.

The mean time of peak plasma concentrations was 1 hour 8 minutes for 200 mg bevantolol, 1 hour 40 minutes for 400 mg bevantolol, and 2 hours 40 minutes for 100 mg atenolol. The $t_{\frac{1}{2}}$ for both doses of bevantolol was approximately 2 hours, but the study period was too short to calculate a precise $t_{\frac{1}{2}}$ for atenolol. There was a good correlation between plasma levels of the β-blockers and the reduction in exercise-induced tachycardia ($r=0.87$ for bevantolol and $r=0.84$ for atenolol). Because 400 mg bevantolol could be regarded as cardioequipotent to 100 mg atenolol, the drugs were used in these doses to compare their ventilatory effects in patients with asthma.

Study in patients with asthma.

There were no significant differences between the initial values of the indices measured on the different days of the study. At rest 2 hours after drug dosing, mean (±SE) heart rate decreased by 10 ± 2.4 bpm after 400 mg bevantolol ($p<0.01$) and by 12.8 ± 2.5 bpm after 100 mg atenolol ($p<0.01$). Systolic blood pressure at rest decreased by 9.5 ± 3.2 mmHg after bevantolol ($p<0.05$) and by 12.3 ± 2.3 mmHg after atenolol ($p<0.01$). There was no significant change in diastolic blood pressure during β-blockade at rest.

Results of the forced expiratory flow measurements are presented in Table II (next page) and Figs. 2 to 4 (pags. 97, 98). Bevantolol 400 mg, induced a decrease in FEV_1 of 1.07 ± 0.26 L and in PEFR of 2.35 ± 0.69 L/sec ($p<0.01$), whereas atenolol and placebo did not decrease these parameters (Table II). MEF_{50} and MEF_{25} fell significantly after both β-blockers, but the decline after bevantolol was significantly larger than that after atenolol. During exercise there was a significant increase ($p<0.01$) in the forced expiratory flow indices measured during placebo, bevantolol, and atenolol dosing (Fig. 2, upper panel).

Fifteen minutes after the second exercise test during atenolol dosing, FEV_1 significantly fell from 2.61 ± 0.24 L before exercise to 1.99 ± 0.21 L after exercise, and PEFR declined from 6.45 ± 0.56 to 5.33 ± 0.62 L/sec (Table II, Fig. 2, lower panel). Bevantolol significantly decreased PEFR after exercise (from 4.63 ± 0.58 to 4.28 ± 0.60 L/sec), whereas FEV_1 did not change. During placebo there were no sig-

TABLE II Ventilatory indices before and after placebo, 400 mg bevantolol, and 100 mg atenolol, after exercise and after inhalation of terbutaline

	Initial values (5 min before dosing)	2 hr after dosing	p value*	2 hr 20 min after dosing (15 min after 2nd exercise test)	P value+	After inhalation of 2 mg terbutaline	P + value+
FEV_1 (L)							
Placebo	2.91±0.31	2.83±0.30	NS	2.60±0.22	NS	3.58±0.29	<0.01
Bevantolol 400 mg	2.87±0.26	1.80±0.21	<0.01	1.70±0.22	NS	2.58±0.31	<0.01
Atenolol 100 mg	2.79±0.26	2.61±0.24	NS	1.99±0.21	<0.01	3.14±0.33	<0.02
PEFR (L/sec)							
Placebo	6.81±0.43	6.53±0.49	NS	6.33±0.45	NS	8.31±0.51	<0.01
Bevantolol 400 mg	6.98±0.56	4.63±0.58	<0.01	4.28±0.60	<0.05	6.49±0.73	<0.01
Atenolol 100 mg	6.33±0.48	6.45±0.56	NS	5.33±0.62	<0.01	8.00±0.80	<0.01
MEF_{50} (L/sec)							
Placebo	2.16±0.42	1.93±0.38	NS	1.79±0.23	NS	3.24±0.55	<0.01
Bevantolol 400 mg	2.05±0.29	0.98±0.16	<0.01	0.99±0.16	NS	1.79±0.28	<0.01
Atenolol 100 mg	1.98±0.35	1.60±0.26	<0.05	1.24±0.17	NS	2.56±0.49	<0.01
MEF_{25} (L/sec)							
Placebo	0.96±0.19	0.81±0.17	NS	0.80±0.08	NS	1.56±0.28	<0.01
Bevantolol 400 mg	0.96±0.15	0.45±0.06	<0.01	0.46±0.05	NS	0.78±0.10	<0.01
Atenolol 100 mg	0.93±0.15	0.76±0.10	<0.05	0.60±0.07	NS	1.15±0.21	<0.01

NS = not significant. * Values 2 hr after dosing vs. initial values.

+ Values 2 hr 20 min after dosing vs. values 2 hr after dosing. + + Values after 2 mg terbutaline vs. values 2 hr 20 min after dosing.

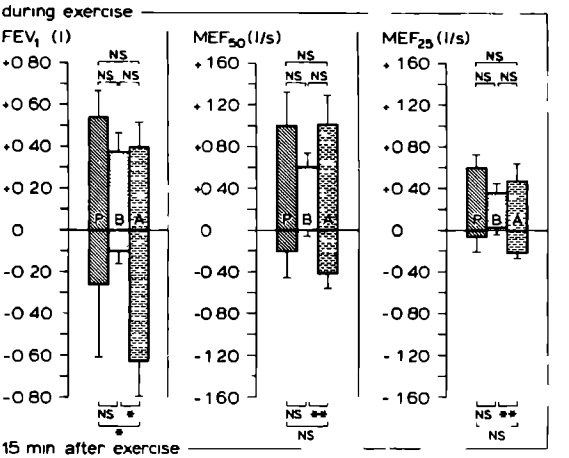

Fig. 2. Mean (±SE;n=8) rise and fall in FEV_1, MEF_{50} and MEF_{25} during and after the second exercise test 2 hours after drug dosing. Measurements were performed during the last minute of exercise (upper panel) and 15 minutes after exercise (lower panel) and differences were calculated from preexercise values 2 hours after drug dosing during placebo (P), 400 mg bevantolol (B), and 100 mg atenolol (A). NS = Not significant; *p<0.05; **p<0.01.

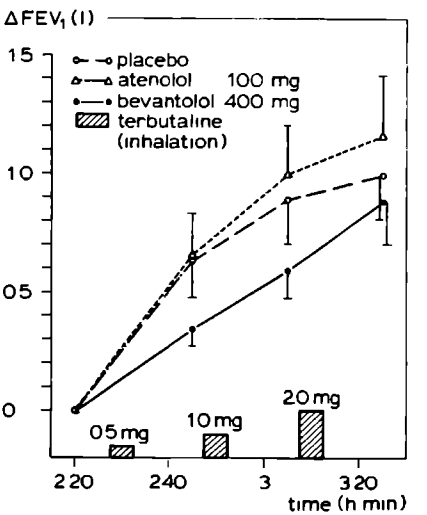

Fig. 3. Mean (±SE,n=8) changes in FEV_1 induced by inhalation of terbutaline in cumulative doses after placebo, 400 mg bevantolol, and 100 mg atenolol.

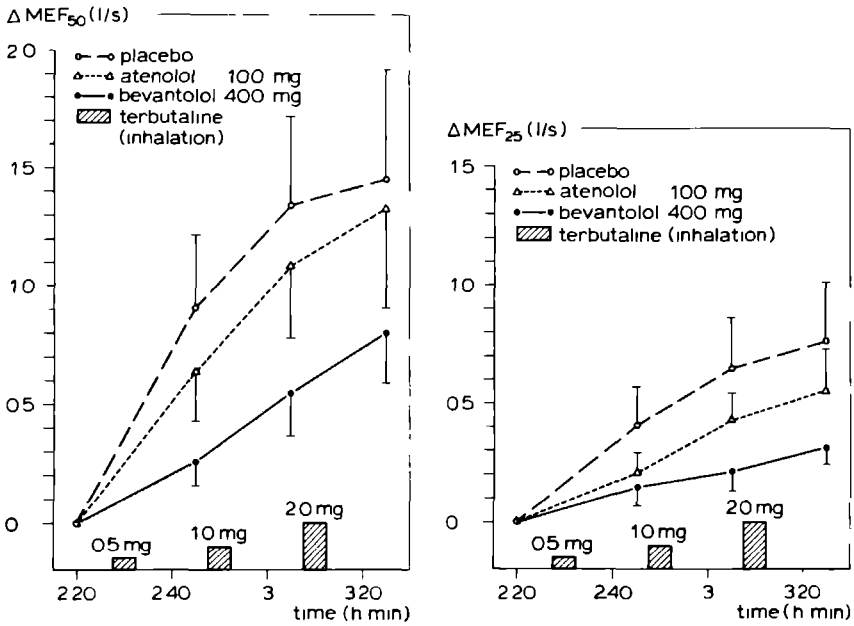

Fig. 4. Mean (±SE;n=8) changes in MEF_{50} and MEF_{25} induced by inhalation of terbutaline in cumulative doses after placebo, 400 mg bevantolol, and 100 mg atenolol.

nificant changes in either FEV_1 or PEFR 15 minutes after exercise (Table II, Fig. 2, lower panel). There were no significant decreases in MEF_{50} and MEF_{25} after exercise as compared with preexercise values during placebo, bevantolol, and atenolol dosing. However, the decrease in MEF_{50} and MEF_{25} after exercise during atenolol dosing was significant as compared with the effect of bevantolol on these indices (Fig. 2, lower panel). The absolute values for FEV_1, PEFR, MEF_{50} and MEF_{25} before and after the second exercise test, 2 hours and 2 hours 20 minutes, respectively after bevantolol dosing, were significantly lower than the corresponding values during placebo and atenolol dosing ($p<0.05$; Table II).

Inhalation of terbutaline up to a cumulative dose of 2 mg significantly increased the ventilatory indices measured (Table II; Figs. 3 and 4). The bronchodilatory effect of terbutaline was smaller during bevantolol dosing than during placebo and atenolol dosing (Figs. 3 and 4). During bevantolol dosing the absolute values of FEV_1, PEFR, MEF_{50}, and MEF_{25} after terbutaline inhalations were almost at the same level as the initial values before drug dosing, whereas during placebo and atenolol dosing the values after terbutaline were significantly higher than the initial values (Table II).

After the second exercise test all patients had at least one minor asthmatic attack. This happened seven times during bevantolol and only once after atenolol. All complaints disappeared immediately after the first inhalation of terbutaline and all patients left the clinical without complaints.

DISCUSSION

From our study in healthy subjects we conclude that 2 hours after drug dosing, 400 mg bevantolol was cardioequipotent to 100 mg atenolol, because at that time both β-blockers induced equal decreases in exercise-induced tachycardia. We therefore used both β-blockers at these two doses to compare their effects on forced expiration parameters. The study was carried out in patients with asthma with >15% reversibility of the FEV_1, because β-blockers usually induce bronchospasm in such patients, while this effect is much smaller or absent in normal subjects and in patients with low reversible or fixed bronchoconstriction[17,18,24]. In the patients with asthma both β-blockers induced the same reduction in heart rate at rest and during exercise, indicating the same degree of cardiac β-blockade. However, the two β-blockers had significantly different effects on lung function.

During bevantolol dosing there was a significant decrease in FEV_1 and PEFR 2 hours after drug dosing before the second exercise test. Atenolol, however, did not induce such a decrease in these large airways parameters at rest. Although both bevantolol and atenolol significantly decreased MEF_{50} and MEF_{25}, the reduction after bevantolol was

larger than that after atenolol. Small airways function at rest, therefore, seems to be more sensitive to β-adrenoceptor blockade than large airway function in these patients with asthma.

The normal rise in airway conductance during exercise, probably due to increased sympathetic tone[12], was not influenced by either bevantolol or atenolol; this is in accord with results of other studies[6,10]. During atenolol dosing there was a significant decrease in FEV_1 and PEFR after exercise in comparison with the preexercise values 2 hours after drug dosing, while the differences in MEF_{50} and MEF_{25} between pre- and postexercise values were not significant. This increase in bronchoconstriction, especially in the larger airways, by exercise was not demonstrated during placebo dosing. During bevantolol dosing there was only a small decrease in PEFR after exercise, while FEV_1 remained unchanged. The different effects of atenolol and bevantolol on bronchomotor tone after exercise are probably explained by the fact that bevantolol had already induced considerable bronchoconstriction before the second exercise test. Therefore, exercise-induced bronchoconstriction can be enhanced by β-adrenoceptor blockade, an effect that seems to depend on the preexercise bronchomotor tone.

During therapy with 400 mg bevantolol the dose-response curves with terbutaline for FEV_1, PEFR, MEF_{50} and MEF_{25} shifted downward in comparison with placebo and atenolol, indicating less β-adrenoceptor selectivity for bevantolol at this dose than for atenolol.[7,9] β-Adrenoceptor selectivity is, however, a dose-dependent phenomenon,[4,13] and a smaller dose of bevantolol might show more β_1-adrenoceptor selectivity.

Acknowledgement

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CHAPTER 7

A COMPARATIVE STUDY ON THE VENTILATORY AND HAEMODYNAMIC EFFECTS OF XAMOTEROL AND ATENOLOL IN ASTHMATIC PATIENTS

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SUMMARY

1. Effects of single oral doses of atenolol 50 mg and xamoterol 200 mg (a recently developed partial β_1-adrenoceptor agonist) on lung function, heart rate and blood pressure were investigated in 11 patients with asthma.

2. The β_1-adrenoceptor selectivity of these drugs was assessed by comparison of dose-response curves of lung function parameters after inhalation of the β_2-adrenoceptor agonist terbutaline.

3. Xamoterol caused a significant increase in heart rate and systolic blood pressure, indicating its partial β_1-adrenoceptor agonist activity.

4. As xamoterol did not cause a bronchodilatation, it appears unlikely that there exists a β_1-adrenoceptor mediated bronchodilatation.

5. Atenolol induced a significant increase in bronchoconstriction, while this occurred only in 3 patients during xamoterol.

6. Atenolol 50 mg and xamoterol 200 mg have a similar degree of β_1-adrenoceptor selectivity.

Keywords: Asthma, atenolol, xamoterol, β_1-adrenoceptor function.

INTRODUCTION

Soon after the introduction of nonselective β-adrenoceptor antagonists it became clear, that these drugs can induce severe bronchospasm in asthmatic patients (McNeill, 1964). The introduction of β_1-adrenoceptor selective antagonists seemed to be an advantage, but this type of β-blockers can also induce bronchoconstriction in asthmatic patients (Greefhorst and Van Herwaarden, 1981; Lammers et al, 1984; Ellis et al, 1981). The decline in lung function after a β_1-adrenoceptor-selective blocker can be explained via two possibilities: β_1-adrenoceptor selectivity is a relative characteristic: increasing the dose leads to a decrease in selectivity (Fleming et al, 1978). Another possibility is that there are apart from β_2-adrenoceptors also β_1-adrenoceptors in the airways by which bronchodilatation is mediated. In-vitro experiments have demonstrated that the ratio of β_2- to β_1-adrenoceptors varies between species (Rugg et al, 1978). Zaagsma et al (1983), however, could only demonstrate a homogeneous β_2-adrenoceptor population in human tracheal and bronchial smooth muscle. Results of experiments in asthmatic patients with prenalterol, a partial β_1-adrenoceptor agonist, are conflicting. Löfdahl and Svedmyr (1982) could not demonstrate a bronchodilator effect of prenalterol in asthmatics, whereas Greefhorst and Van Herwaarden (1983) on the contrary were able to demonstrate an increase in vital capacity after prenalterol in asthmatic patients. Xamoterol (ICI 118,587) was shown in animal experiments to exhibit a higher β_1-adrenoceptor selectivity as prenalterol (Cook et al, 1984) and this compound has substantial partial β_1-adrenoceptor agonist activity (Nuttall and Snow, 1982; Rousseau et al, 1983). It seems therefore of interest to investigate if the β_1-adrenoceptor agonist activity of xamoterol has an effect on the lung function of asthmatic patients. We also compared the β_1-adrenoceptor selectivity of xamoterol with the β_1-adrenoceptor selectivity of a low dose of atenolol in the same group of patients.

METHODS

Eleven male patients with bronchial asthma (American Thoracic Society, 1962) completed the study. Some clinical details are given in Table 1 (next page). Their mean age was 36.6 years, their mean height 176.9 cm and their mean weight 73.7 kg. Five of them were cigarette smokers, the others being nonsmokers. There were 7 patients with atopic extrinsic asthma with one or more positive skin tests to inhalational allergens. None of the patients suffered from cardiovascular diseases. Their ventilation was moderately to mildly disturbed: the forced expiratory volume in one second (FEV_1) ranged from 40 to 74% of the predicted normal value (Quanjer, 1983). In all patients FEV_1 increased 15% or more after stimulation with a β_2-adrenoceptor agonist. Bronchodilator medication was stopped at least 12 hours before the start of the first measurement on each study day. Cromoglycate and beclomethasone were not inhaled on the days of investigations. All patients refrained from smoking and drinking caffeine containing beverages 24 hours before each study period. The study was approved by the local Ethics Committee and written informed consent was obtained from each patient before entry into the study.

The investigations were performed on 3 different days. Placebo was given single-blind on the first day. On the 2 other days the patients received double-blind and in random order xamoterol 200 mg and atenolol 50 mg. Between the study days 2 and 3 there was an interval of at least 4 days to serve as a washout period. All measurements started at noon to minimize the effects of diurnal rhythm in airway conductance which frequently occurs in asthmatics (Connolly, 1979). The study drugs were administered orally before a standard meal to avoid differences in bioavailability within each subject (Melander et al, 1977).

Before and 2 hours after drug intake the following measurements were performed after a resting period of at least 30 minutes: forced vital capacity (FVC), FEV_1 and peak expiratory flow rate (PEFR) were derived from maximal expiratory flow-volume curves which were measured with a Fleisch nr 4 pneumotachograph. Heart rate (HR) was recorded with an electrocardiograph (Hellige) and blood pressure (BP) was assessed with the cuff-method (mean of 2 readings; Korotkoff phase 5).

TABLE 1 Patient characteristics

Subject	Age (yrs)	Smoking history	Asthma type*	Height (cm)	Weight (kg)	FEV_1 actual (l)	FEV_1 % of predicted values	FEV_1 % increase with terbutaline	Therapy**
1	58	+	I	161	68	1.50	55	30	-
2	47	-	I	182	94	2.68	68	25	B S
3	32	-	I	188	74	3.40	74	19	-
4	25	-	E	171	66	1.70	40	29	S
5	24	+	E	178	61	2.60	57	29	-
6	43	+	E	178	92	2.25	58	18	B S
7	38	-	E	169	54	1.70	47	50	C S
8	22	-	E	180	63	2.60	58	35	S
9	60	+	I	174	80	2.28	70	15	S
10	23	-	E	185	78	3.70	74	24	S
11	31	+	E	180	81	2.50	57	44	S
mean ±SEM	36.6±4.2			176.9±2.3	73.7±3.8	2.45±0.2	59.8±3.3	28.9±3.2	

* E = extrinsic; I = intrinsic
**B = beclomethasone; C = cromoglycate; S = salbutamol
FEV_1 = forced expiratory volume in one second (l)

The values of the measurements obtained before drug intake are referred to as baseline values. Subsequently, dose-response curves with a β_2-adrenoceptor agonist were performed by assessing HR, BP and flow-volume curves 15 minutes after inhalation of increasing doses of terbutaline. Terbutaline was administered with a metered dose inhaler in cumulative doses of 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg. In order to facilitate inhalation, terbutaline was inhaled through a Nebuhaler^R (Astra), being a cone-shaped extension device of 750 ml (Newman et al, 1981). The results are presented as mean $\pm$ SEM. For statistical analysis the Wilcoxon test for paired observations was used. Statistical significance was defined as $p<0.05$ (Colton, 1974).

RESULTS

No significant differences were found between the baseline values of the indices measured on the different days of the study. The effects of xamoterol and atenolol on the baseline values of HR and BP are shown in Figure 1 (upper panel). HR increased significantly by 10.8 $\pm$ 2.1 beats/min ($p<0.01$) 2 hours after intake of xamoterol and decreased significantly by 9.4 $\pm$ 1.5 beats/min ($p<0.01$) after atenolol. Xamoterol caused an increase in systolic BP of 7.4 $\pm$ 2.0 mmHg ($p<0.01$), whereas after atenolol systolic BP decreased by 8.3 $\pm$ 1.5 mmHg ($p<0.01$). All three study drugs caused a significant fall in diastolic BP. The decline in diastolic BP after xamoterol and atenolol did not differ significantly from the effect of placebo on this parameter.

The changes in lung function parameters 2 hours after drug intake, as compared to the baseline values of the same day, are presented in Table 2 (page 111) and Figures 1 (lower panel) and 2 (page 109). Atenolol caused a mean decrease in FVC of 0.35 l and in FEV_1 of 0.35 l, both changes being significant. There was a tendency towards a decrease in mean FVC and FEV_1 during xamoterol, but this mean change was, however, not significant. This effect of xamoterol on FVC and FEV_1 was caused by a decrease of more than 20% of baseline values in 3 of 11 patients, as is shown for FEV_1 in Figure 2. The mean PEFR did not change significantly which was mainly due to intra- and interindivi-

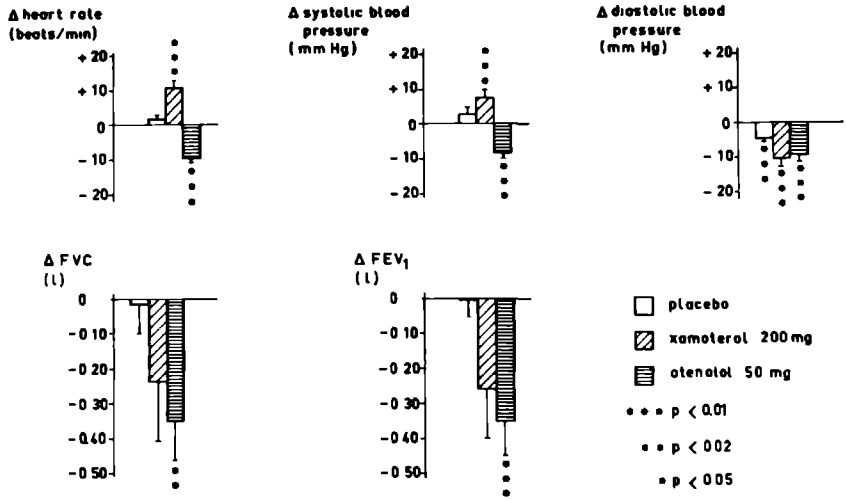

Fig. 1 Changes in haemodynamic and ventilatory indices 2 hours after intake of placebo, xamoterol 200 mg and atenolol 50 mg, as compared to baseline values (mean ± s.e.mean).
* $p<0.05$; ** $p<0.02$; *** $p<0.01$.

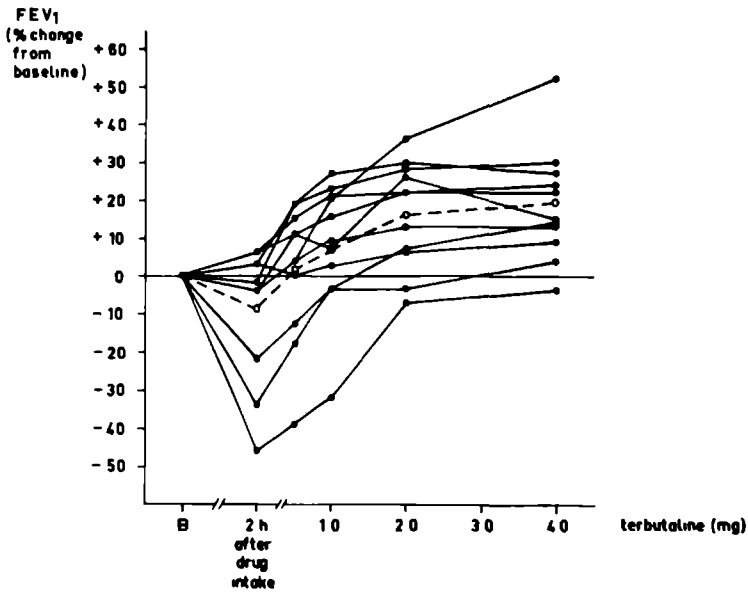

Fig. 2. Individual changes of FEV_1, expressed as % change from baseline, 2 hours after intake of xamoterol 200 mg and after subsequent inhalation of cumulative doses of terbutaline. 0---0 represents mean values.

dual variations of this parameter. The variability found in this study, however, did not exceed the variability as described in the literature (Quanjer, 1983).

Inhalation of terbutaline up to a cumulative dose of 4.0 mg had no effect on HR or systolic BP. Also diastolic BP did not change after terbutaline during placebo. However, diastolic BP did increase significantly after 4.0 mg terbutaline during atenolol by 7.1 $\pm$ 3.1 mmHg ($p<0.02$) and during xamoterol by 9.9 $\pm$ 2.2 mmHg ($p<0.01$).

The effects of terbutaline on lung function are shown in Table 2 (next page) and Figure 3 (page 113). A significant improvement in FVC, FEV_1 and PEFR was found during placebo, atenolol and xamoterol. Comparison of the increases in FVC and FEV_1 by terbutaline did not reveal significant differences between placebo, atenolol or xamoterol (Fig. 3). There was, however, a significant difference after maximal stimulation with terbutaline between the absolute FEV_1 values of placebo and atenolol ($p<0.02$) and the FEV_1 values of placebo and xamoterol ($p<0.05$), whereas there was no such significant difference between xamoterol and atenolol (Table 2).

DISCUSSION

The purpose of this study was to investigate the effects of xamoterol, a partial β_1-adrenoceptor agonist (Nuttall and Snow, 1982; Rousseau et al, 1983) on lung function, HR and BP in comparison with placebo and atenolol, a β_1-adrenoceptor-selective antagonist (Ellis et al, 1981; Lammers et al, 1985). The study was performed in asthmatic patients with a reversibility of their FEV_1 of at least 15%, because these patients are more susceptible for the bronchoconstrictor effects of β-adrenoceptor antagonists as patients with a lower reversibility of their airways obstruction (Perks et al, 1978).

As we were interested to see whether the intrinsic sympathomimetic activity of xamoterol has any effect on lung function, the patients were studied at rest, since it is shown that xamoterol acts as a β-adrenoceptor agonist at low levels of sympathetic tone, but as a β-adrenoceptor antagonist when sympathetic tone is high, as during exer-

TABLE 2 Ventilatory parameters before and after intake of placebo, atenolol and xamoterol and after cumulative doses of terbutaline (mean ± s.e.mean)

		baseline values	values 2h after drug intake	p*	values after inhalation of terbutaline 0.5mg	p+	1.0mg	p+	2.0mg	p+	4.0mg	p+
FVC (1)												
placebo		4.58±0.31	4.56±0.28	NS	4.85±0.30	NS	5.01±0.30	<0.02	5.05±0.27	<0.01	5.11±0.30	<0.01
atenolol	50 mg	4.58±0.29	4.24±0.30	<0.02	4.66±0.28	<0.01	4.79±0.29	<0.01	4.95±0.28	<0.01	5.00±0.28	<0.01
xamoterol	200 mg	4.60±0.27	4.35±0.32	NS	4.72±0.32	<0.01	4.84±0.32	<0.01	5.31±0.31	<0.01	5.05±0.32	<0.01
FEV_1 (1)												
placebo		2.89±0.27	2.88±0.28	NS	3.17±0.32	<0.05	3.43±0.31	<0.01	3.59±0.31	<0.01	3.74±0.31	<0.01
atenolol	50 mg	2.84±0.30	2.49±0.28	<0.01	2.95±0.33	<0.01	3.12±0.34	<0.01	3.33±0.34	<0.01	3.37±0.34	<0.01
xamoterol	200 mg	2.95±0.24	2.69±0.31	NS	3.04±0.36	<0.01	3.23±0.36	<0.01	3.45±0.35	<0.01	3.53±0.35	<0.01
PEFR (1/s)												
placebo		6.95±0.64	7.13±0.72	NS	8.04±0.75	<0.02	8.52±0.78	<0.01	9.01±0.76	<0.01	9.37±0.91	<0.01
atenolol	50 mg	7.36±0.72	6.84±0.75	NS	7.97±0.89	<0.05	7.85±0.98	NS	9.06±0.87	<0.01	9.14±0.90	<0.01
xamoterol	200 mg	7.98±0.81	6.83±0.73	NS	7.76±0.94	<0.05	8.42±1.00	<0.01	8.99±0.90	<0.01	9.14±0.88	<0.01

p*: values 2 h after drug intake vs baseline values.

p^+: values after inhalation of terbutaline vs values 2 h after drug intake.

NS: not significant.

cise (Harry et al, 1981; Rousseau et al, 1983; O'Neill et al, 1984). HR and systolic BP were significantly decreased by atenolol 50 mg, while there was a significant increase in these parameters after xamoterol 200 mg (Figure 1). Xamoterol therefore has at rest an inotropic effect, as shown by others previously (Rousseau et al, 1983; Löfdahl and Svedmyr, 1984). The effects of xamoterol and atenolol on diastolic blood pressure were probably mediated by rest, since diastolic blood pressure also declined after placebo. Atenolol 50 mg induced a clear bronchoconstriction as can be concluded from the decrease in FVC and FEV_1 (Table 2 and Figure 1). In a previous study (Lammers et al, 1985) we did not find an effect of atenolol 100 mg on FEV_1 in asthmatic patients at rest. After exercise, however, there was a significant fall in FEV_1 during atenolol 100 mg. It remains therefore unpredictable how an asthmatic patient will react to even a low dose of a β_1-adrenoceptor selective antagonist and the β-adrenoceptor selectivity of these drugs appears to be not completely dose-dependent as suggested by Ellis et al (1981) and Fleming et al (1978).

Xamoterol induced an increase in HR and systolic BP, which effect is β_1-adrenoceptor mediated. On the contrary, xamoterol did not improve lung function and it seems therefore unlikely that there exists a β_1-adrenoceptor mediated bronchodilatation. This appears to correlate well with radioligand binding studies in vitro, as Zaagsma et al (1983) could not demonstrate β_1-adrenoceptors in human bronchial smooth muscle. Conversely, it seems that bronchoconstriction induced by β_1-adrenoceptor-selective blockers must be explained by a lack of selectivity of these drugs and not by a blockade of β_1-adrenoceptors in the bronchial smooth muscles.

Xamoterol caused a bronchoconstriction in 3 patients, as can be concluded from the fall in their FEV_1 (Figure 2). Although these 3 patients had a reversibility of FEV_1 of more than 25%, other patients with a high reversibility did not show a decrease in lung function after xamoterol. Löfdahl and Svedmyr (1984) also described a fall of more than 20% in 2 out of 8 asthmatic patients after an intravenous dose of xamoterol 0.1 mg/kg.

The improvement in lung function after inhalation of terbutaline was similar for atenolol, xamoterol and placebo (Table 2, Figure 3).

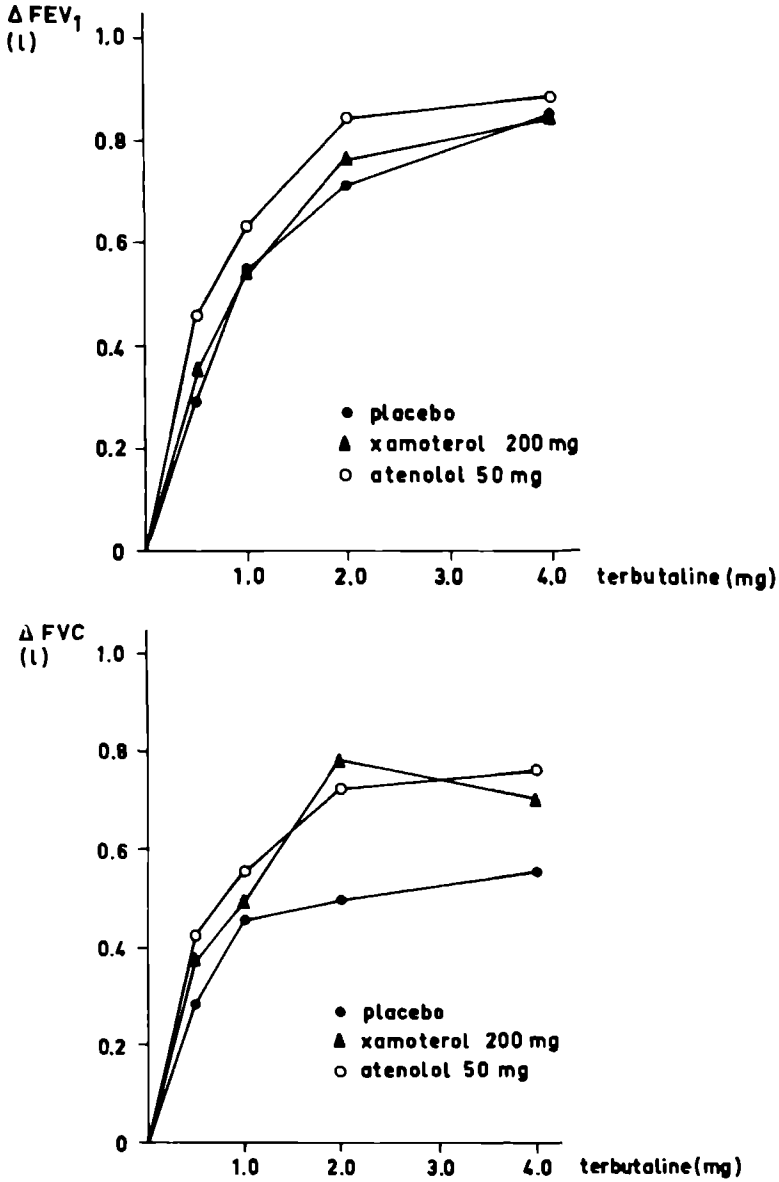

Figure 3. Mean changes in FVC and FEV_1 induced by terbutaline in cumulative doses as compared to values 2 hours after intake of placebo (●), xamoterol 200 mg (▲) and atenolol 50 mg (o).

As dose-response curves with a β_2-adrenoceptor agonist during β-blockade are indicative for the β-adrenoceptor selectivity of these drugs (Johnsson et al, 1975; Lammers et al, 1985), it can be concluded from Figure 3 that xamoterol 200 mg has similar β_1-adrenoceptor selectivity as atenolol 50 mg. Nevertheless, both drugs should be used with care in asthmatic patients and only when concomitantly β-adrenoceptor agonists are administered.

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Chapter 8

EFFECTS OF TERBUTALINE AND ATENOLOL ON LARGE AND SMALL AIRWAYS IN ASTHMATIC PATIENTS

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Submitted for publication

SUMMARY

In order to localize the main site of action of the β_2-adrenoceptor selective agonist terbutaline and the β_1-adrenoceptor selective antagonist atenolol in the airways of asthmatic patients, we compared the effects of these drugs on maximal expiratory flow-volume (MEFV) curves when breathing air and when breathing a helium-oxygen ($He-O_2$) mixture. To investigate whether a shift in localization of the bronchodilator effect occurs when terbutaline is inhaled repeatedly, dose-response curves with terbutaline were performed for parameters derived from MEFV-curves when breathing air and for density dependence of expiratory airflow.

Atenolol caused constriction of large and small airways as measured with MEFV-curves when breathing air. Inhalation of terbutaline to a cumulative dose of 2.0 mg induced a stepwise improvement in expiratory airflow parameters for large and small airways function, when breathing air. Doubling the dose to 4.0 mg did not result in any further improvement of lung function. Neither atenolol nor terbutaline did induce significant mean changes in density dependence of expiratory airflow. This was partly due to large inter- and intraindividual variations of this parameter. Another possibility is that atenolol and terbutaline equally affected large and small airways function.

INTRODUCTION

Ventilatory effects of β-adrenoceptor agonists and antagonists are usually assessed with routine lung function tests, such as measurement of total airway resistance, peak expiratory flow rate (PEFR), and the forced expiratory volume in one second (FEV_1). Although these methods give insight in changes in overall lung function, they do not distinguish between the effects of these drugs on large or small airways. By measurement of airflow at high and low lung volumes, which can easily be performed with flow-volume curves, a distinction between the effects of drugs on large or small airways can be made (Mead et al, 1967; Chick and Jenne, 1977; Pride, 1979). A further distinction be-

tween the influence of drugs on large or small airways can probably be made by comparison of flow-volume curves, when the patient is breathing air and when he is breathing a low-density gas mixture like $He-O_2$ (Despas et al, 1972).

This assessment of density dependence has been used to determine the site of bronchodilatation by β-adrenoceptor agonists and/or cholinergic antagonists (Ingram et al, 1977; Minette et al, 1985; Fairshter et al, 1981; Ashutosh et al, 1980). These studies concerned the bronchodilator effect of a single oral or inhaled dose of a bronchodilator. We wondered if the consecutive administration of a β_2-adrenoceptor agonist would induce a shift in the localization of the bronchodilator effect in asthmatic patients.

As there is little information on the localization of the bronchoconstriction induced by β-adrenoceptor antagonists in asthmatics, we investigated also the effect of atenolol, a β_1-adrenoceptor selective antagonist, on forced expiratory airflow parameters and density dependence in the same group of asthmatic patients.

METHODS

Eleven male patients aged 22 to 60 years, were studied. All suffered from asthma as defined by the American Thoracic Society (1962). Their mean height was 176.9 cm (range 161-188 cm) and their mean weight 73.7 kg (range 54-94 kg). Five patients were smokers and 7 were allergic to one or more inhalational allergens. Their lung function was mildly to moderately disturbed: the FEV_1 ranged from 40 to 74% of the predicted normal value (Quanjer, 1983). All patients had shown an increase in their FEV_1 of at least 15% after inhalation of a β_2-adrenoceptor agonist before they entered the study. They were in a stable phase of their disease and none of them required oral corticosteroids or theophylline-derivatives. Eight patients used salbutamol by inhalation as bronchodilator medication; this was not used for at least 12 hours prior to the first measurement. Two patients inhaled beclomethasone dipropionate and 1 patient cromoglycate regularly; these drugs were not inhaled on the days of investigation. The study was approved by

the local Ethics Committee and written informed consent was obtained from each patient.

Lung function parameters were obtained from maximal expiratory flow-volume (MEFV) curves, which were obtained with a flow-volume equipment containing a Fleisch No. 4 pneumotachograph. Before each set of measurements the flow-volume equipment (Discom, Chest Company Tokyo) was calibrated separately with room air and a mixture of 80% helium and 20% oxygen ($He-O_2$). Volume history was standardized by maximal inhalation to total lung capacity (TLC) prior to the performance of all MEFV-curves. First, three MEFV-curves were obtained when breathing room air. Next, $He-O_2$ was washed in during 4 minutes when breathing this gas from a Douglas bag and thereafter a second set of three MEFV-curves was obtained. The air MEFV-curves with the best sum of forced vital capacity (FVC) and FEV_1 (Gardner, 1977) were used for calculations of FVC, FEV_1, PEFR and maximal expiratory flow rate when 50% and 25% of the FVC still were to be expired (MEF_{50} and MEF_{25} respectively). The $He-O_2$ MEFV-curves with the best fitting FVC's compared to the air MEFV-curves were used for calculation. We used as parameter for density dependence ΔMEF_{50}:

$$\Delta MEF_{50} = \frac{MEF_{50}(He-O_2) - MEF_{50}(air)}{MEF_{50}(air)} \times 100\%$$

(Despas et al, 1972; Dosman et al, 1975).
The volume of isoflow ($V_{iso\ V}$) was calculated after superimposing the air and $He-O_2$ MEFV-curves at the level of residual volume (Hutcheon et al, 1974; Dosman et al, 1975).

The investigations were performed on two different days. After assessment of baseline lung function at 12.00 AM study drugs were administered by mouth. On the first day placebo was given single-blind and at the second occasion atenolol 50 mg, both as identical tablets. At 02.00 PM lung function measurements were repeated. Thereafter, a dose-response curve with the β_2-adrenoceptor agonist terbutaline was performed by obtaining air and $He-O_2$ MEFV-curves 15 minutes after inhalation. Terbutaline was inhaled four times through a 750 ml spacer (Nebuhaler^R) from a metered dose inhaler (Newman et al, 1981) in cumu-

Wilcoxon test for paired observations was used. Statistical significance was defined as $p<0.05$.

RESULTS

Baseline values for the different lung functions measured are given in the table (page 123). No significant differences were found between these values between the two days of investigation.

There were no changes in lung function parameters 2 hours after intake of placebo (Table). However, atenolol 50 mg caused a significant fall in FVC, FEV_1, MEF_{50} and MEF_{25}. Density dependence and V_{iso} V were not influenced by atenolol.

Inhalation of terbutaline caused a significant improvement in FVC, FEV_1, PEFR, MEF_{50} and MEF_{25} ($p<0.01$), both during placebo and atenolol 50 mg (Table). Dose-response curves with terbutaline for MEF_{50} and MEF_{25} are presented in Fig. 1 (next page). There was no significant difference between the dose-response curves during placebo and atenolol for both parameters.

The effects of consecutive inhalations of terbutaline on ΔMEF_{50} are shown in Figs. 2 and 3 (page 124). There was a tendency towards an increase in ΔMEF_{50} after inhalation of 0.5 mg terbutaline during placebo (Fig. 2). This difference was, however, not significant. As can be seen in Fig. 3, where the effects of terbutaline on ΔMEF_{50} during placebo treatment have been separated between smokers and nonsmokers, this small change in ΔMEF_{50} mainly occurred in the smoking patients. Further inhalation of terbutaline up to a cumulative dose of 4.0 mg did not influence ΔMEF_{50}, either during placebo or during atenolol 50 mg. There also was no change in V_{iso} V after inhalation of terbutaline (Table).

DISCUSSION

The effects of atenolol and terbutaline on the FEV_1 and PEFR in this group of asthmatic patients have been described in detail in Chapter 7.

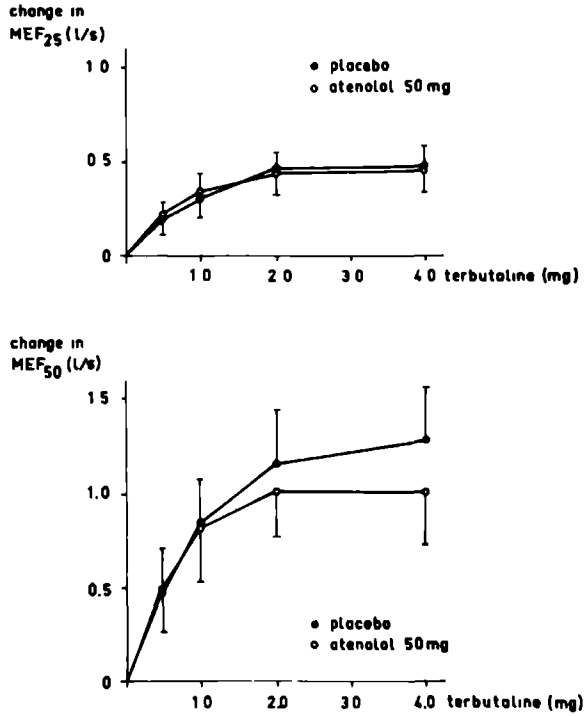

Figure 1. Changes in MEF_{50} and MEF_{25} induced by inhalation of terbutaline in cumulative doses as compared to values 2 hours after intake of placebo (•) and atenolol 50 mg (o) (mean $\pm$ SEM, n=11).

Since FEV_1 and PEFR are mainly determined by the resistance in the larger airways (Gelb and Klein, 1977; Pride, 1979), it appears that atenolol caused a constriction and terbutaline a dilatation of the larger airways. Atenolol 50 mg also caused a constriction of smaller airways as is indicated by the significant fall in MEF_{50} and MEF_{25} (Pride, 1979; Minette et al, 1985; Chick and Jenne, 1977).

Inhalation of terbutaline up to a cumulative dose of 2.0 mg resulted in a steady increase in MEF_{50} and MEF_{25} during both placebo and atenolol (Fig. 1). Madsen et al (1983) suggested from the results of their study that for an effect on smaller airways of terbutaline a higher dose is required that for an effect on FEV_1. We were not able to confirm their findings. After inhalation of 2 mg terbutaline a plateau was reached for FEV_1, MEF_{50} and MEF_{25} during both placebo and a-

TABLE Ventilatory parameters before and 2 h after intake of placebo and atenolol and after inhalation of 4 mg terbutaline (mean±SEM, n=11).

		PLACEBO					ATENOLOL				
		baseline values	2 h after drug intake	P*	after 4 mg terbutaline	P+	baseline values	2 h after drug intake	P*	after 4 mg terbutaline	P+
FVC	(l)	4.58±0.31	4.56±0.28	NS	5.11±0.30	<0.01	4.58±0.29	4.24±0.30	<0.02	5.00±0.28	<0.01
PEFR	(l/s)	6.95±0.64	7.13±0.72	NS	9.37±0.91	<0.01	7.36±0.72	6.84±0.75	NS	9.14±0.90	<0.01
FEV_1	(l)	2.89±0.27	2.88±0.28	NS	3.74±0.31	<0.01	2.84±0.30	2.49±0.28	<0.01	3.37±0.34	<0.01
MEF_{50}	(l/s)	2.11±0.33	2.11±0.35	NS	3.39±0.55	<0.01	2.10±0.35	1.70±0.29	<0.01	2.75±0.53	<0.01
MEF_{25}	(l/s)	0.85±0.14	0.86±0.15	NS	1.34±0.23	<0.01	0.86±0.16	0.66±0.12	<0.01	1.11±0.22	<0.01
ΔMEF_{50}	(%)	38.7±5.0	31.1±8.2	NS	38.3±5.5	NS	30.6±6.8	36.8±7.3	NS	48.2±4.0	NS
$V_{iso\ V}$	(%FVC)	81.2±5.1	79.6±5.0	NS	79.6±4.4	NS	81.1±5.2	76.0±4.3	NS	81.6±2.9	NS

P* = baseline values versus values 2 h after drug intake.

P+ = values 2 h after drug intake versus values after terbutaline.

NS = not significant.

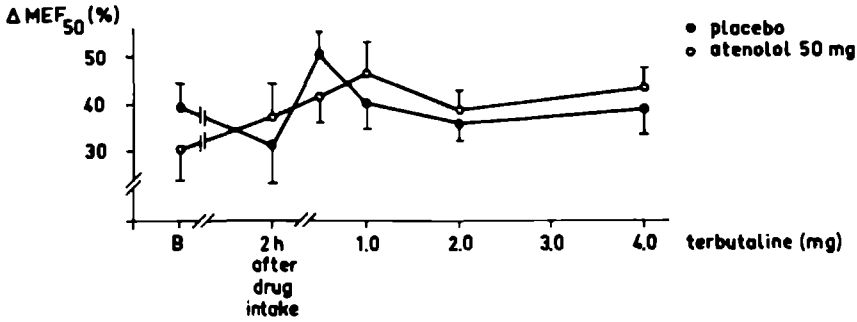

Figure 2. Effects of terbutaline in cumulative doses on ΔMEF_{50} during placebo (•) and atenolol 50 mg (o) (mean ± SEM; n=11).

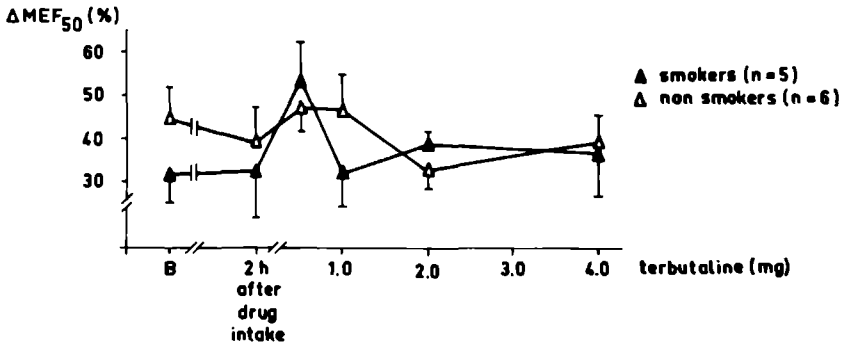

Figure 3. Effects of terbutaline in cumulative doses on ΔMEF_{50} during placebo in smokers (▲) and non smokers (Δ) (mean ± SEM).

tenolol, indicating a simultaneous dilatation of large and small airways by terbutaline.

Despas et al (1972) introduced the measurement of density dependence as a method to assess the main localization of obstruction in the airways of patients with asthma and chronic bronchitis. A density dependence of less than 20% indicates that the major site of obstruction is located in small peripheral airways, while a density dependence of more than 20% is compatible with mainly large airways obstruction (Despas et al, 1972; Dosman et al, 1975).

Later on, Hutcheon and coworkers (1974) and Dosman et al (1975) described the volume of isoflow as another method to discriminate between large and small airways function.

A volume of isoflow, at which the MEFV-curves when breathing air and when breathing $He-O_2$ coincide, of more than 80% is assumed to demonstrate that the major site of bronchoconstriction is located in larger airways. Both parameters have been used to assess the main site of action of bronchoconstrictor and bronchodilator agents. Several authors (Minette et al, 1985; Ashutosh et al, 1980; Hensley et al, 1978; Ingram et al, 1977; Chick and Jenne, 1977; Fairshter et al, 1981) mentioned a different localization of the bronchodilator effects of cholinergic antagonists and β-adrenoceptor agonists. While the former mainly give dilatation of larger airways, the latter would preferentially dilate smaller airways.

In our patients the β_1-adrenoceptor selective antagonist atenolol did not affect mean density dependence or the mean value of the volume of isoflow. By this method, therefore, no distinction could be made between the effects of atenolol on large or small airways.

During placebo, there was no significant change in density dependence or the volume of isoflow after inhalation of terbutaline. There was, however, a tendency towards a mean increase in density dependence after inhalation of 0.5 mg terbutaline in smoking patients (Fig. 3). This small rise in ΔMEF_{50} was followed by a decrease after further inhalation of terbutaline. From these results it seemed that bronchodilatation by terbutaline first occurred in the smaller airways of these smoking asthmatics and after a higher dose shifted to larger airways. These changes were, however, not significant and the small

number of smoking patients (5) prohibits too many conclusions. Moreover, at every point in the dose-response curves of ΔMEF_{50} of all patients, there were large intraindividual and interindividual variations resulting in mean values with high standard errors. Other authors (Bonsignore et al, 1980; Mc Donald and Cole, 1980; Berend et al, 1981) also described a large variability of density dependence and $V_{iso\ V}$. Recently, it has been suggested that sites of flow limitation, airway geometry and patterns of flow may differ with the density of the respired gas (Mink and Wood, 1980; Knudson and Schroter, 1983), and it therefore remains questionable whether this method is reliable enough to localize bronchodilatation and bronchoconstriction.

On the other hand, it is possible that asthmatic patients do not have a uniform pattern in their reactions to bronchoconstrictor and bronchodilator stimuli.

Another possibility might be that atenolol and terbutaline causes proportionately equal constriction and dilatation of large and small airways, leaving density dependence relatively unchanged (Ingram et al, 1977).

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CHAPTER 9

SUMMARY AND CONCLUSIONS

SUMMARY

The main components of the autonomic nervous system of the lung and airways are the parasympathetic or cholinergic system and the sympathetic or adrenergic system. The latter can be subdivided into the α-adrenergic and the β-adrenergic system. An imbalance between the excitatory cholinergic and the α-adrenergic system on the one hand and the inhibitory β-adrenergic system on the other hand is supposed to be an important factor in the pathogenesis of asthma.

In the studies presented in this thesis we approached the function of the pulmonary β-adrenergic system in patients with chronic nonspecific lung disease (CNSLD) from a clinical-pharmacological point of view. In this respect we studied the effects of β-adrenoceptor blockade and stimulation on the lung function of patients with asthma and chronic obstructive bronchitis.

Chapter 1 presents a general introduction with an outline of the studies reported in this thesis.

In Chapter 2 we describe some aspects of the autonomic regulation of the lung and airways. There is ample evidence that cholinergic efferent nerves which travel through the vagal nerves, innervate bronchial smooth muscles and mediate bronchoconstriction. In normal subjects there is some vagal bronchomotor tone, but in patients with asthma the cholinergic influence is much more pronounced. In contrast to a rich cholinergic nerve supply, the adrenergic innervation of the human lung is sparse. The bronchoconstrictor and bronchodilator action of β-adrenoceptor antagonists and agonists respectively, in asthmatic patients has to be explained by interaction with β-adrenoceptors on the airway smooth muscles. The presence of a high density of these β-adrenoceptors has been documented by radioligand binding studies and recently by means of autoradiography. The β-adrenoceptors can functionally be divided into β_1- and β_2-subtypes. From the results of in-vitro experiments it appears that the human bronchial smooth muscles contain a homogeneous population of β_2-adrenoceptors. Nonselective β-blockers antagonize both β_1- and β_2-adrenoceptors. Since blockade of

β_2-adrenoceptors in airway smooth muscles of asthmatic patients results in bronchoconstriction, nonselective β-adrenoceptor antagonists can cause bronchospasm in these patients by blockade of β_2-adrenoceptors in the airway smooth muscles. However, β_1-adrenoceptor-selective blocking agents can also induce some bronchoconstriction, especially in larger doses. It has been suggested that the β-adrenergic system may modulate vagal bronchomotor tone by interference at the level of the cholinergic ganglia in the airway wall. Blockade of β_2-adrenoceptors and possibly also of β_1-adrenoceptors at this location may enhance cholinergic-mediated bronchoconstriction. This theory, however, is still unproven and a more probable explanation of the bronchoconstriction caused by β_1-adrenoceptor selective blockers seems to be a lack of selectivity of these compounds.

A third nervous system in the lung, the so-called nonadrenergic, noncholinergic system, has also been described, but the function of this inhibitory system is not yet well defined.

In **Chapter 3** we review several methods to assess the effects of β-adrenoceptor agonists and antagonists on dynamic lung function in patients with CNSLD. Functionally, the airway system can be divided into large and central airways on the one hand, and small or peripheral airways on the other. Total airway resistance and peak expiratory flow rate (PEFR) are parameters which mainly give information on the function of the larger airways. The forced expiratory volume in one second (FEV_1) is also largely determined by the calibre of the larger airways, although changes in smaller airways can influence FEV_1 to some extent. Frequency dependence of lung compliance and closing volume are parameters which are sensitive to changes in small airways, but only when other lung function tests are normal. Maximal expiratory flow-volume (MEFV) curves, on the other hand, seem to provide an easily performed method to determine large and small airways function at the same time, also when routine lung function tests such as FEV_1 are abnormal. Especially the assessment of density dependence, being the difference between MEFV-curves when breathing air and those when breathing a low-density gas mixture (80% helium and 20% oxygen), has gained interest for the localization of the effects of drugs in the

airways. The substantial variability of this method, however, is a disadvantage.

Comparative studies of the bronchoconstrictor effects of different β-adrenoceptor blockers and their interaction with the bronchodilator action of a β_2-adrenoceptor agonist in patients with asthma have proved to be a good model to assess the β_1-adrenoceptor selectivity of β-blockers in man.

In Chapter 4 we describe a double-blind, placebo-controlled study of the bronchoconstrictor effects and β_1-adrenoceptor selectivity of metoprolol, a well-known β_1-selective blocker, and bisoprolol, a recently developed β-adrenoceptor antagonist in asthmatic patients. Because 100 mg metoprolol appears to be cardioequipotent to 10 mg bisoprolol, these doses were compared. Also 20 mg bisoprolol was studied to see whether the β_1-adrenoceptor selectivity of this drug was diminished at a higher dosage. Both β-blockers caused bronchoconstriction as indicated by a significant fall in PEFR. Decreases in vital capacity (VC) and FEV_1 were significant only during 10 mg bisoprolol. Inhalation of the β_2-adrenoceptor agonist terbutaline induced immediate bronchodilatation both during placebo treatment and during the three β-blocker doses. There was no difference in the shape and position of the terbutaline dose-response curves of FEV_1 and PEFR during placebo or any of the β-blockers. Both β-blockers caused equally significant decreases in heart rate (HR), and 20 mg bisoprolol and 100 mg metoprolol also caused a significant fall in systolic and diastolic blood pressure (BP). Inhalation of terbutaline to a cumulative dose of 3.5 mg had no effect on HR and BP. These results indicate good β_1-adrenoceptor selectivity of 100 mg metoprolol and 10 mg and 20 mg bisoprolol.

Ventilatory effects of β-blockers in patients with CNSLD are usually assessed in single-dose studies.
In Chapter 5 we describe a comparative double-blind, cross-over study of the effects of long-term treatment with the β_1-adrenoceptor-selective antagonist metoprolol and the nonselective β-blocker with intrinsic sympathomimetic activity (ISA) pindolol in patients with CNSLD

and concomitant hypertension. Bronchodilator therapy was continued throughout the study period. There were no changes in daily measured PEFR or pulmonary complaints during treatment with both β-blockers. There was a small, but significant decrease in FEV_1 during metoprolol, but not during pindolol. This difference can probably be explained by the effect of the ISA of pindolol on the β_2-adrenoceptors in the airways. The β_2-adrenoceptor agonist terbutaline induced significant bronchodilatation during placebo and metoprolol but not during pindolol treatment. This disparity can be explained by the nonselective character of pindolol. There were no changes in the parameters of small airways function in this group of patients, either during placebo or during treatment with one of the β-blockers. Moreover, terbutaline did not influence the small airways parameters, which may be due to structural changes in the smaller airways of these patients. We concluded from this study that, if a β-adrenoceptor blocker is necessary in patients with CNSLD, a β_1-adrenoceptor-selective blocker is to be preferred in combination with bronchodilator agents such as β_2-adrenoceptor agonists, and under regular monitoring of lung function.

Chapter 6 discusses the effects of β-adrenoceptor blockade at rest and during and after exercise on large and small airways function. For this purpose the effects of the β_1-adrenoceptor-selective blocker atenolol on dynamic lung function parameters were compared with those of a cardioequipotent dose of a new β-blocker, bevantolol, in asthmatic patients with reversible airways obstruction. The interaction of both β-blockers with the β_2-agonist terbutaline was also studied. At rest, bevantolol caused generalized bronchoconstriction, whereas atenolol induced only some obstruction of smaller airways. However, after exercise atenolol also caused large airways obstruction. The bronchodilator effect of terbutaline was similar during placebo and atenolol treatment but was attenuated during bevantolol. It was therefore concluded that atenolol is more β_1-adrenoceptor-selective than bevantolol in the doses used in this study. However, exercise can enhance the effects of β_1-adrenoceptor selective antagonists on lung function and therefore these β_1-selective blockers should be used with care, or not at all, in patients with readily reversible airways obstruction. The

normal rise in airway conductance during exercise was not attenuated by β-adrenoceptor blockade. It therefore seems doubtful whether this rise in expiratory airflow parameters is caused by a higher level of sympathetic tone during exercise, as often suggested.

Chapter 7 discusses the question whether there exists a β_1-adrenoceptor mediated bronchodilatation and/or bronchoconstriction. For this purpose we studied the ventilatory effects of xamoterol, a recently developed partial β_1-adrenoceptor agonist, on lung function in 11 asthmatic patients at rest. To assess the β_1-adrenoceptor selectivity of this compound we compared dose-response curves of dynamic lung function parameters upon inhalation of terbutaline during xamoterol, placebo and the β_1-adrenoceptor-selective antagonist atenolol. After 200 mg xamoterol 3 patients showed a decrease in FEV_1, while atenolol caused more pronounced bronchoconstriction. Several patients who did not show a decrease in FEV_1 after 100 mg atenolol during a previous study showed an increase in bronchoconstriction after 50 mg atenolol in the present study. The question therefore remains whether β_1-adrenoceptor selectivity is really a dose-dependent phenomenon. Other factors such as hyperreactivity of the airways, may also influence the effect of a β_1-adrenoceptor-selective blocker on the airways of asthmatic patients.

Dose-response curves with terbutaline were assessed by inhalation of cumulative doses through a 750 ml spacer (Nebuhaler^R, Astra), which proved to be an effective method. Xamoterol (200 mg) showed the same β_1-adrenoceptor selectivity as 50 mg atenolol. Since xamoterol did not induce bronchodilatation, it appears unlikely that there exists β_1-adrenoceptor-mediated bronchodilatation.

It has been suggested in the literature that the bronchodilator and bronchoconstrictor effects of drugs can be differentiated as to a more central or a more peripheral action in the airways. In order to localize the main site of action of the β_2-adrenoceptor-selective agonist terbutaline and the β_1-adrenoceptor-selective antagonist atenolol in the airways of asthmatic patients, we compared the effects of these drugs on maximal expiratory flow-volume (MEFV) curves when breathing

air and when breathing a helium-oxygen mixture (Chapter 8). Atenolol and terbutaline caused constriction and dilatation of large and small airways, respectively, as measured with MEFV-curves when breathing air. Neither atenolol nor terbutaline induced significant mean changes in density dependence (ΔMEF_{50}) of expiratory airflow. We found large intra- and interindividual variations in this parameters, which may cast some doubt on the usefulness of this method to localize the major site of action of drugs in the airways. On the other hand, it is possible that asthmatic patients do not have a uniform pattern in their reactions to bronchoconstrictor and bronchodilator stimuli. Another possibility is that atenolol and terbutaline equally affected the functions of large and small airways, leaving density dependence relatively unchanged.

CONCLUSIONS

1. The β_1-adrenoceptor selectivity of β-blockers is a relative characteristic.

2. β_1-Adrenoceptor stimulation by exogeneously administered β_1-adrenoceptor agonists does not cause bronchodilatation.

3. The increase in forced expiratory airflow during exercise is not caused by an increase in sympathetic tone.

4. A clear separation between the effects of β_2-adrenoceptor-selective stimulation on the function of large or small airways in asthmatic patients could not be assessed.

5. If a β-adrenoceptor blocking agent is required in patients with CNSLD, a β_1-adrenoceptor selective blocker is to be preferred with concomitant use of β_2-adrenoceptor agonists and under regular monitoring of lung function.

SAMENVATTING EN CONCLUSIES

Astma, chronisch obstructieve bronchitis en emfyseem behoren tot een groep longziekten, welke meestal aangeduid wordt als chronisch aspecifieke respiratoire aandoeningen (CARA). Deze algemene term is geïntroduceerd, omdat genoemde ziektebeelden vaak beschouwd worden als verschillende uitingsvormen van één syndroom, waarbij gemeenschappelijke oorzaken een rol spelen. Bovendien kunnen bij CARA-patiënten de ziekteverschijnselen in de tijd variëren, en de verschillende ziektebeelden zijn vaak moeilijk of niet van elkaar te onderscheiden.

In **Hoofdstuk** 1 is aangeduid, dat meerdere factoren tot CARA kunnen leiden. Een stoornis in de regulatie van de functie van longen en luchtwegen door het autonome zenuwstelsel wordt vaak als één van deze factoren genoemd.

Hoofdstuk 2 beschrijft een aantal aspecten van de autonome regulatie van longen en luchtwegen. De belangrijkste componenten hiervan zijn het parasympathische of cholinerge systeem en het sympathische of adrenerge systeem. Er zijn voldoende aanwijzingen, dat cholinerge zenuwvezels vanuit het centrale zenuwstelsel en lopende via de nervus vagus, de gladde spieren van de luchtwegen innerveren. Bij gezonde personen lijkt er altijd enige tonus (spanning) in deze bronchiale gladde spieren aantoonbaar te zijn, wat door cholinerge activiteit veroorzaakt wordt. Bij astmapatiënten is dit echter meer uitgesproken. De menselijke long heeft een rijke cholinerge zenuwvoorziening, maar slechts een spaarzame adrenerge innervatie. De luchtwegvernauwende en -verwijdende effecten van respectievelijk β-adrenoceptor blokkerende en stimulerende geneesmiddelen bij astmapatiënten kunnen verklaard worden door koppeling met zogenaamde β-adrenoceptoren, die op de gladde spiercellen van de luchtwegen aanwezig zijn. De aanwezigheid van een groot aantal van deze β-adrenoceptoren is aangetoond met behulp van zogenaamde radioligand binding studies en recentelijk door middel van autoradiografie. De β-adrenoceptoren kunnen functioneel ingedeeld worden in twee subtypen: de β_1- en de β_2-adrenoceptoren. Uit radioligand binding studies blijkt dat de gladde spiercellen

van menselijke luchtwegen alleen het β_2-subtype bevatten. Blokkade van deze β_2-adrenoceptoren leidt tot luchtpijpvernauwing (bronchoconstrictie) bij astmapatiënten. β-Adrenoceptor blokkerende geneesmiddelen worden veelvuldig gebruikt bij hart- en vaatziekten, zoals hypertensie en angina pectoris. De niet-selectieve β-blokkers blokkeren zowel β_1- als β_2-adrenoceptoren en kunnen dus bij astmapatiënten bronchoconstrictie veroorzaken. β_1-Adrenoceptor selectieve blokkeerders blokkeren voornamelijk de β_1-adrenoceptoren. Dit type β-blokker blijkt echter ook bronchoconstrictie te kunnen veroorzaken, zij het meestal pas in hogere doseringen. De meest waarschijnlijke verklaring hiervoor lijkt te zijn, dat de β_1-adrenoceptor selectiviteit een relatieve eigenschap is. Bij ophogen van de dosis gaat de β_1-adrenoceptor selectiviteit gedeeltelijk verloren en worden er ook β_2-adrenoceptoren geblokkeerd. Anderzijds wordt er wel gesuggereerd dat het β-adrenerge systeem in de long een remmende invloed uitoefent op het bronchoconstrictief werkende cholinerge systeem. Stimulatie van β_1- en/of β_2-adrenoceptoren, gelegen in of op de cholinergia ganglia in de bronchuswand, zou een vermindering geven van de cholinerge zenuwprikkelgeleiding. Blokkade van deze β-adrenoceptoren door β-blokkers daarentegen zou de cholinerge bronchoconstrictie kunnen versterken. Vooralsnog zijn er echter onvoldoende gegevens om deze laatste hypothese te bewijzen.

In **Hoofdstuk 3** worden enige methoden beschreven om de effecten van β-adrenerge blokkerende en stimulerende geneesmiddelen op de longfunctie te meten. Functioneel gezien kan het luchtwegsysteem onderverdeeld worden in centrale of grotere luchtwegen enerzijds en perifere of kleinere luchtwegen anderzijds. Er worden een aantal longfunctietesten beschreven, waarvan er enige voornamelijk de functie van de grotere luchtwegen weergeven en andere meer gevoelig zijn voor veranderingen in de kleinere luchtwegen. Ook worden methoden beschreven waarmee gelijktijdig de functie van grotere en kleinere luchtwegen bepaald kan worden.

Middels de studies in dit proefschrift hebben wij de functie van het β-adrenerge systeem bij CARA-patiënten benaderd vanuit een klinisch-

farmacologisch gezichtspunt. Daartoe werden de effecten onderzocht van β-adrenoceptor blokkade en stimulatie op de longfunctie van patiënten met astma en chronisch obstructieve bronchitis.

Vergelijkend onderzoek naar de effecten van verschillende β-blokkers op de longfunctie van astmapatiënten geeft, vooral wanneer dit gecombineerd wordt met toediening van β_2-adrenoceptor stimulerende middelen, inzicht in de mate van β_1-adrenoceptor selectiviteit van deze β-blokkers.
In **Hoofdstuk 4** wordt een dergelijk onderzoek beschreven naar de β_1-adrenoceptor selectiviteit van de al langer bekende β_1-adrenoceptor selectieve blokker metoprolol en de recentelijk ontwikkelde β-blokker bisoprolol. De β-blokkers veroorzaken enige bronchoconstrictie, welke snel opgeheven kan worden door inhalatie van de β_2-adrenoceptor stimuleerder terbutaline. Beide β-blokkers bezitten derhalve een goede mate van β_1-adrenoceptor selectiviteit in de onderzochte doseringen.

Effecten van β-blokkers op de luchtwegen van patiënten met CARA worden meestal bestudeerd na een eenmalige toediening van een β-blokker. Voor de dagelijkse praktijk is langduriger gebruik echter minstens zo belangrijk, mede gezien het feit dat er in de literatuur gesuggereerd wordt, dat de negatieve invloed van deze geneesmiddelen op de longfunctie kan toenemen bij regelmatig gebruik.
In **Hoofdstuk 5** worden de resultaten besproken van een vergelijkend onderzoek naar de effecten van de β-blokkers metoprolol en pindolol op de longfunctie van CARA-patiënten, nadat beide middelen gedurende een maand gebruikt zijn. Tijdens de studieperiode worden bronchusverwijdende geneesmiddelen vrijwel onveranderd gecontinueerd. De pulmonale klachten van de patiënten blijken niet nadelig beïnvloed te worden door behandeling met de onderzochte β-blokkers. Wel worden er bij longfunctiemeting kleine verschillen tussen beide β-blokkers geconstateerd, die toegeschreven worden aan verschillende eigenschappen van de twee onderzochte β-blokkers. De resultaten van dit onderzoek wijzen erop, dat in uitzonderlijke gevallen β-blokkerende behandeling mogelijk is bij patiënten met CARA. De voorkeur gaat dan uit naar een β_1-adrenoceptor selectief middel met gelijktijdig gebruik van bron-

chusverwijdende geneesmiddelen. Bovendien is regelmatige longfunctiecontrole aangewezen.

Hoofdstuk 6 beschrijft een onderzoek naar de effecten van β-adrenoceptor blokkade en stimulatie op grotere en kleinere luchtwegen van patiënten met astma. Tevens wordt het gecombineerde effect van β-adrenoceptor blokkade en inspanning onderzocht. In rust veroorzaakt de β_1-adrenoceptor selectieve blokker atenolol alleen constrictie van kleinere luchtwegen. Na inspanning veroorzaakt atenolol echter een algehele bronchoconstrictie. De nieuwe β-blokker bevantolol veroorzaakt in rust al een constrictie van grotere en kleinere luchtwegen, welk effect niet versterkt wordt door inspanning. In de in dit onderzoek gebruikte doseringen lijkt atenolol een hogere β_1-adrenoceptor selectiviteit te bezitten dan bevantolol. Normaliter treedt er tijdens inspanning een toename op van de geforceerde uitgeademde luchtstroom (expiratoire flow). β-Adrenoceptor blokkade verhindert deze stijging in expiratoire flow niet. Dit fenomeen lijkt derhalve niet, zoals aangenomen wordt, veroorzaakt te worden door een hogere activiteit van het β-adrenerge systeem tijdens inspanning.

Zoals beschreven, wordt het bronchoconstrictieve effect van een β_1-adrenoceptor selectieve blokker enerzijds toegeschreven aan een gebrek aan β_1-adrenoceptor selectiviteit van deze middelen, anderzijds bestaat de mogelijkheid dat blokkade van β_1-adrenoceptoren in de luchtwegen tot bronchoconstrictie leidt. Om de eventuele functie van β_1-adrenoceptoren in de luchtwegen nader te evalueren, hebben wij de invloed onderzocht van een β_1-adrenoceptor stimulerend middel, xamoterol, op de longfunctie van astmapatiënten (Hoofdstuk 7). Uit de resultaten van dit onderzoek blijkt, dat β_2-adrenoceptor stimulatie wel bronchusverwijding veroorzaakt, maar dat β_1-adrenoceptor stimulatie door middel van xamoterol geen bronchusverwijding tot gevolg heeft. Een lage dosis van de β_1-adrenoceptor blokker atenolol daarentegen veroorzaakt in dezelfde patiëntengroep een duidelijke bronchoconstrictie. Dit wordt waarschijnlijk veroorzaakt door blokkade van β_2-adrenoceptoren door atenolol, daar selectiviteit een relatieve eigenschap is. De vraag of zuivere β_1-adrenoceptor blokkade wel of niet tot bronchoconstrictie aanleiding kan geven, is vooralsnog onbeantwoord.

Hoofstuk 8 beschrijft een studie naar de effecten van de β_1-adrenoceptor selectieve blokkeerder atenolol en de β_2-adrenoceptor selectieve stimuleerder terbutaline op de grotere en kleinere luchtwegen van astmapatiënten. Geen van beide middelen blijkt een duidelijke voorkeur te hebben voor grotere of kleinere luchtwegen. Atenolol veroorzaakt een gegeneraliseerde bronchusvernauwing en terbutaline een gegeneraliseeerde bronchusverwijding. Gezien de variabiliteit van de resultaten van één van de gebruikte meetmethoden, is het discutabel of deze methode wel geschikt is voor het onderscheiden van de effecten van geneesmiddelen op grotere of kleinere luchtwegen.

CONCLUSIES

1. De β_1-adrenoceptor selectiviteit van β-blokkers is een relatieve eigenschap.
2. β_1-Adrenoceptor stimulatie middels exogeen toegediende β_1-adrenoceptor agonisten leidt niet tot bronchodilatatie.
3. De stijging van de geforceerde expiratoire luchtstroom tijdens inspanning wordt niet veroorzaakt door een verhoogde sympathicotonus.
4. Er is geen duidelijke scheiding mogelijk van de effecten van β-adrenoceptor selectieve stimulatie op de functie van enerzijds de grotere en anderzijds de kleinere luchtwegen van astmapatiënten.
5. Wanneer behandeling van CARA-patiënten met een β-blokker noodzakelijk is, dan dient een β_1-adrenoceptor selectieve blokker voorgeschreven te worden in combinatie met een β_2-adrenoceptor agonist. Regelmatige longfunctie-controle is dan eveneens vereist.

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De auteur van dit proefschrift werd op 13 juni 1953 geboren te Nijmegen. In 1971 behaalde hij het diploma gymnasium β aan het St. Canisius College te Nijmegen. Daarna studeerde hij geneeskunde aan de Katholieke Universiteit te Nijmegen. Gedurende deze studie was hij bijna 3 jaar werkzaam als student-assistent in het Instituut voor Geschiedenis der Geneeskunde van deze universiteit (hoofd: prof. dr. D. de Moulin). In 1974 verrichtte hij gedurende 4 maanden wetenschappelijk onderzoek in de Department of Physiology, University of Pennsylvania te Philadelphia, U.S.A. (prof. dr. S.Y. Botelho). In februari 1979 werd het artsexamen afgelegd en begon hij met de opleiding tot internist in de Kliniek voor Inwendige Ziekten van de Katholieke Universiteit te Nijmegen (hoofd destijds: prof. dr. C.L.H. Majoor, nadien prof. dr. A. van 't Laar). Op 1 november 1981 begon hij de opleiding tot longarts in het Universitair Longcentrum te Nijmegen (hoofd: prof. C.M. Jongerius) en op 1 november 1984 volgde de inschrijving in het specialistenregister. Sindsdien is hij verbonden als longarts aan het Universitair Longcentrum, bestaande uit de afdelingen longziekten van het Sint Radboudziekenhuis te Nijmegen en het Medisch Centrum Dekkerswald te H. Landstichting.

STELLINGEN

behorend bij het proefschrift

Beta-adrenoceptor blockade and stimulation in obstructive lung disease

J-W.J. LAMMERS

I

Bronchodilatatie tijdens inspanning wordt niet veroorzaakt door een verhoogde activiteit van het sympathische zenuwstelsel.

(Dit proefschrift)

II

Beta$_1$-adrenoceptor stimulatie veroorzaakt geen bronchodilatatie.

(Dit proefschrift)

III

In het zeldzame geval dat aan CARA-patiënten een beta-blokker voorgeschreven dient te worden, biedt een beta-blokker met intrinsieke sympathicomimetische activiteit geen voordelen boven een beta-blokker zonder deze eigenschap.

(Dit proefschrift)

IV

Bronchiale hyperreactiviteit kan aangetoond worden door middel van inhalatieprovocatietesten of inspanningsonderzoek. Registratie van de flow-volume curve verdient hierbij de voorkeur boven het gebruik van de Wright peak-flow meter.

V

Een obstructieve longfunctiestoornis is slechts dan irreversibel te noemen, wanneer met intensieve bronchodilaterende behandeling, waaronder systemische toediening van corticosteroïden, geen verbetering van de longfunctie bereikt kan worden.

VI

Bij de symptomatische behandeling van het centraal gelocaliseerde obstruerende bronchuscarcinoom dienen lasercoagulatie en/of het plaatsen van een endobronchiale buisprothese tenminste overwogen te worden.

(J. Festen et al. Ned Tijdsch Geneesk 128: 214-217, 1984)

(Eigen ervaring)

VII

Ook incidenteel gebruik van nasale insufflatie-corticosteroïden kan effectief zijn bij allergische rhinitis.

(Eigen waarneming)

VIII

Indien het nicotineverbruik door vrouwen niet snel afneemt, zal de langere levensverwachting van deze sekse in rook opgaan.

IX

Anorectale spasme bij proctalgia fugax kan opgeheven worden door inhalatie van een beta$_2$-adrenoceptor agonist.

(J.E. Wright, Lancet II: 659-660, 1985)

X

De ontdekking van de spermatozoa van de mens wordt vaak ten onrechte toegeschreven aan Anthonie van Leeuwenhoek in plaats van aan de medisch student Johan Ham (1651-1725).

(J-W.J. Lammers, Ned Tijdsch Geneesk 118: 784-788, 1974)

XI

Patiënt, behandelend specialist en geconsulteerde specialist zijn gebaat bij vroegtijdige aanvraag van pre-operatieve behandelingsadviezen.

XII

De Koninklijke Nederlandse Lawn Tennis Bond zal de speelvreugde van menig tennisspeler verhogen door te voorkomen dat competitiewedstrijden op wisselende baansoorten gespeeld moeten worden.

XIII

Nakaarten na een bridgespel wordt vaak ten onrechte aangegrepen als een gelegenheid om de eigen partner te overtroeven.

J-W.J. Lammers 18 april 1986